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THE DIAGNOSIS AND TREATMENT OF COMPLETE ANOMALOUS PULMONARY VENOUS DRAINAGE

BY

W. T. MUSTARD*

From the Hospital for Sick Children, Toronto

Anomalous pulmonary venous drainage, expressed in the simplest of terms, means that pulmonary veins fail to enter the left auricle. If one or two pulmonary veins fail to enter the left side of the heart there may be no outward signs of cardiac disability and the patient leads a relatively normal life. Even if one half of the oxygenated blood enters directly or by venous channels into the right auricle there may be very few symptoms. However, more than half the venous drainage from the lungs entering the right side of the heart will constitute some disability, and total anomalous pulmonary venous drainage in which no pulmonary veins enter the left atrium is usually accompanied by a poor prognosis and death in infancy. In order to survive there must be an intracardiac communication, usually intra-atrial, in the form of a patent foramen ovale or intra-auricular septal defect. The intracardiac shunt is obviously from right to left, and survival beyond infancy will depend largely on the size of this communication between the two auricles.

An embryological study of this lesion is interesting since it concerns not only the rudimentary systemic venous return but also the venous return of the lungs. In early developmental stages, the lungs, which are considered to develop by division of the foregut, are drained by umbilico-vitelline veins which in turn enter the systemic pre-cardinal and post-cardinal veins. The post-cardinal veins unite to form the inferior vena cava and the pre-cardinal veins the right superior vena cava. While these systemic channels are becoming delineated into the normal situation, a channel from the sinal atrial region of the primitive heart tube outpouches to become the left atrium which grows towards the lungs and develops a communication which eventually forms the normal pulmonary venous drainage.

If one were to postulate that, at the stage at which the pre-cardinal veins are busy disappearing and the outgrowth of the left atrium is equally busy trying to reach the lungs, growth in these venous channels were to stop, then one is left with the left atrium trying in vain to reach the lungs and the lungs quite happy with their drainage into the systemic system of veins. If such a situation persisted it would result in total anomalous pulmonary venous drainage in which the pulmonary veins entered the embryological cardinal venous system. Partial interruption would result in one or more veins making an anastomosis with the outpouching of the left atrium. The venous channels connecting the lungs to the systemic venous system would become elongated and develop into recognizable channels. Due to the disappearance of certain parts of the systemic venous channels there persists a common vein which drains the pulmonary veins and enters the right auricle by way of established systemic venous channels (Fig. 1).

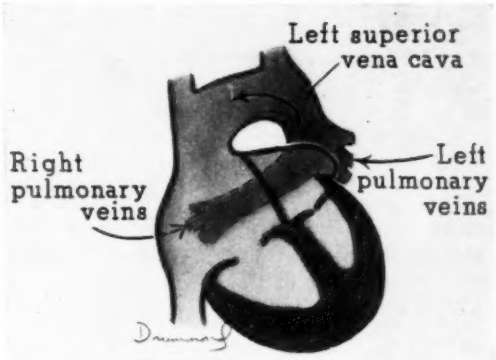

FIG. 1.—Schematic illustration of the pulmonary veins entering the persistent left superior vena cava rather than the left auricle.

Fortunately, Snellen and Albers (1952), closely followed by Gardner and Oram (1953), suspected that this condition could be diagnosed clinically if the presence of a common venous channel was recognized both by clinical investigation and by radiography. Brown (1950) and Whitaker (1954) have contributed in drawing attention to this

* Alex Simpson Smith Memorial Lecture, 1956, given at The Hospital for Sick Children, Great Ormond Street, London.

1

anomaly. Darling and Rothney (1956) have defined accurately the clinical pathology. If complicated cardiac anomalies can be excluded, an isolated form of anomalous pulmonary venous drainage, total in nature, which can be classified either supracardiac, cardiac, infracardiac and mixed, can be recognized.

Fortunately for the surgeon, almost 50% of cases of total anomalous pulmonary venous drainage are supracardiac and drain into a common venous channel, which, on a clinical basis, can be described as a persistent left superior vena cava or a precardinal vein. Unfortunately, to be a true precardinal vein, it should drain into the sinus venosus, but this is not necessarily true. Drainage into the sinus venosus or coronary sinus is at a cardiac level and drainage into the ductus venosus and the portal system is intracardiac. The mixed type, which is exceedingly rare, can be a combination of these forms.

As this anomaly is recognized by pathologists, the incidence may increase, since at necropsy, if the heart is removed from its pericardial sac and it lifts free, an anomalous pulmonary venous drainage is certainly there because of the loss of the tethering effect of the pulmonary veins entering the left atrium. At necropsy, both right ventricle and right auricle are enlarged, the extreme dilatation of the right ventricle masking, to some effect, hypertrophy.

The intra-atrial communication is usually a patent foramen ovale (75% of cases) but may be a large secondary intra-auricular septal defect. The ductus arteriosus is patent in approximately 25% of patients. The pulmonary artery is larger than normal, usually one and a half times the diameter of the aorta. The tricuspid valve ring is larger than the right mitral valve ring and the diameter of the common pulmonary vein, which drains into the right auricle, may be twice the diameter of the waist of the left auricle—of some consideration when one entertains the possibility of surgical approach. One-third of cases show intimal thickening and evidence of pulmonary hypertension. This anomaly probably represents, to the best of our knowledge, 2% of all cardiac malformations in infancy and childhood.

The haemodynamics of this condition are interesting. Pulmonary venous blood of high oxygen saturation enters the right auricle through the common venous channel and mixes with systemic blood of lower saturation, and a variable proportion of both streams passes from the right auricle through a defect in the auricular septum (either a patent foramen ovale or an auricular septal defect) to the left heart and aorta. Also a proportion passes through the tricuspid valve to the right ventricle and out through the pulmonary artery. For this reason the oxygen saturation of the blood in the heart and the systemic circulation is approximately the same.

When one considers the clinical features of this isolated form of total anomalous pulmonary venous drainage, there are certain signs or symptoms during the first two years of life. The first symptom is usually one of tachypnoea. Cyanosis is usually absent in the next few weeks or a month. The infant fails to gain weight satisfactorily and becomes intermittently cyanosed. Distinct cyanosis, gross tachypnoea or failure demands further investigation in the older infant. A typical case is dystrophic and dyspnoeic. Equivocal cyanosis produces a muddy discoloration. Clubbing is rare. The liver is usually enlarged and the praecordium bulging. One-third of cases show no murmurs. A systolic murmur along the sternal border may be present and occasionally a soft continuous venous hum, due to turbulence in the common venous channel, can be discovered.

Radiographically, increased lung vascularity, progressive cardiac enlargement, a left-sided aorta and a 'snowman' appearance, due to the persistence of a left superior vena cava, develop around 4 months of age (Fig. 2). This appearance is described in the English literature as a 'cottage loaf' appearance. The difference in nomenclature is possibly climatic in origin. Most Englishmen have never made a snowman and most Canadians think a cottage loaf is a summer vacation.

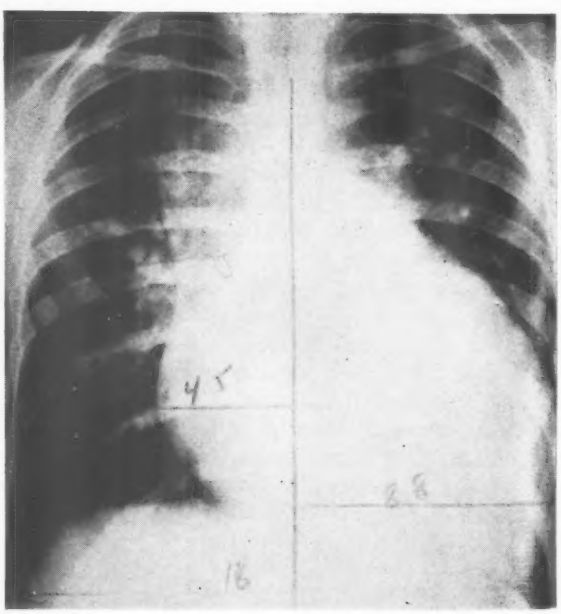

FIG. 2.—'Cottage loaf' appearance due to persistent superior vena cava.

Electrocardiographic tracings show a uniform pattern: right axis deviation, high p waves, right ventricular hypertrophy and q wave in the right praecordial lead.

Cardiac catheterization demonstrates oxygen saturation high in the right auricle and in the superior vena cava. An increase in right auricular pressure, double the average mean pressure, is usually present, and pressure is increased in the pulmonary artery to, or nearly to, systemic level. Occasionally, exploration by catheter may reveal anomalous pulmonary venous drainage entering the left innominate vein (Fig. 3).

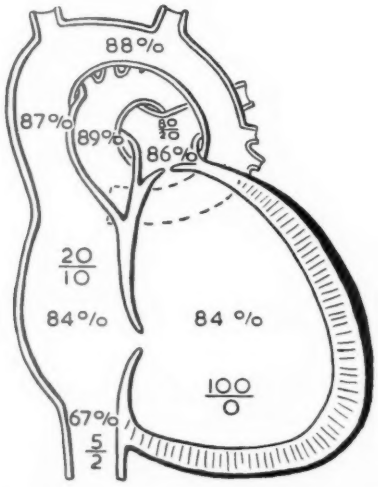

FIG. 3.—Oxygen saturation in total anomalous pulmonary venous drainage.

Indication dilution techniques, after injection of Evans blue into a peripheral vein, may demonstrate a short appearance time with a double tip characteristic of right-to-left shunt.

With the physician cognizant of the condition and the diagnosis confirmed, exploration by thoracotomy is indicated. In our early cases, an anterior approach was used, but more recently we have favoured a lateral approach, somewhat posterior in the fourth interspace on the left side.

Our first three cases in 1952 were operated on at normothermic temperatures. One case was operated on at the extracorporeal circuit using a pump and biological oxygenator. Since that time we have used hypothermia, cooling down to 31° C. and allowing a drift to 28° C. Since these are infants they are cooled in a water bath; over the age of 3 years we use a cooling blanket.

It has been our experience that a common venous channel is immediately seen and dissection is carried down both extra- and intrapericardially to expose this common venous channel with the pulmonary veins entering it, and the waist of the left atrium is brought up (Fig. 4). We feel that it is unwise to

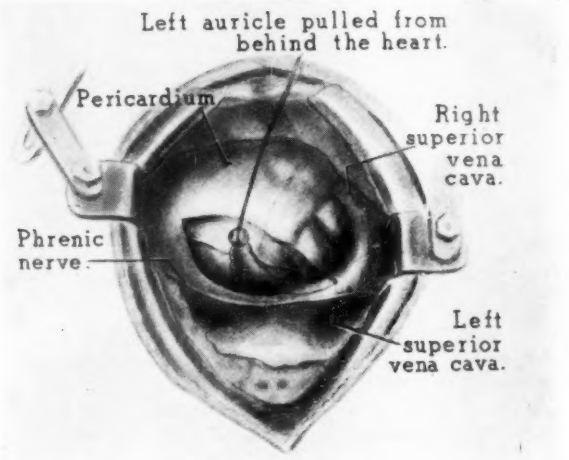

FIG. 4.—Appearance of this anomaly as seen at operation with a posterior-lateral incision in left chest.

anastomose the atrial appendage to the common venous channel because of the size of the waist of the left auricle, which in most cases is only one-half the diameter of the common venous channel. In order to obtain a large anastomosis, the waist of the left atrial appendage is divided longitudinally, which, when it becomes open after anastomosis, will be roughly one and one-half times its normal size. The occlusion of the left atrium in its entirety, including its appendage, and of the venous return from the lungs required, in our opinion, the added protection of hypothermia. Side-to-side anastomosis is carried out, and the surgeon is always tempted and has indeed, on many occasions, tied off the communication to the right auricle via the persistent left superior vena cava (Fig. 5).

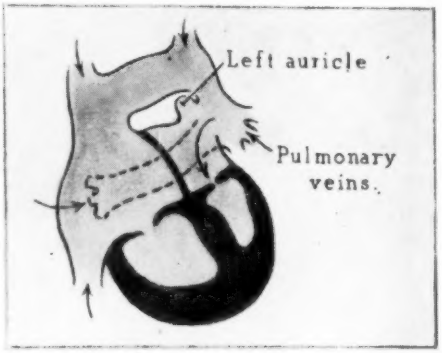

FIG. 5.—Anastomosis between the common venous pool and the waist of the auricle.

Of our first case surviving operation, in 1954, we have no follow-up study as the patient died two months post-operatively with an ear infection. In this patient the superior vena cava had been ligated. On discharge from hospital the patient was in excellent condition. Our subsequent experience with cardiac irregularity and death after ligation of the superior vena cava led us to believe that the persistent superior vena cava should not be ligated, and in our seventh case in 1954 this was not done and the baby, operated upon at 3 months, is thriving and well two years post-operatively. This experience led us, in our eighth case, to leave the vena cava open and re-catheterization of this patient five months post-operatively showed no evidence of right-to-left shunt. The oxygen saturation in both the superior and inferior vena cava was normal (superior vena cava 63%; inferior vena cava 75%). A large volume left-to-right shunt was present between the auricles and indicated the presence of an auricular septal defect. A gain of 10 lb. in weight, lack of symptoms and reduction in right heart strain in the E.C.G. indicated that the new haemodynamic situation of an isolated septal defect was much better tolerated than the combination of total anomalous pulmonary venous drainage and auricular septal defect.

In our next three cases, we became foolishly brave and ligated the superior vena cava. These patients died and demonstrated a relatively small intra-atrial septal defect and a patent foramen ovale. We then felt that it would be unwise to tie the superior vena cava in any case because of the size of the left heart and its inability to withstand the additional load of all the pulmonary venous return to it.

In our last case in February of this year we were fortunate in that it was a mixed lesion in which the left pulmonary vein entered the persistent left superior vena cava and all other veins entered the coronary sinus. We anastomosed the auricular appendage to the persistent left superior vena cava and then ligated it. The waist of the left auricle was then anastomosed to the coronary sinus. This child is alive and well and has not been re-catheterized.

In conclusion I should like to comment upon this interesting condition of total anomalous pulmonary venous drainage and its possible surgical correction. With experience of 12 patients operated upon, four of whom survived operation, one dying two months post-operatively, and three alive and well, we feel justified in making certain recommendations.

First, the diagnosis, since total anomalous pulmonary venous drainage represents 2% of cardiac anomalies, should be made more frequently both on the clinical and radiological findings. Secondly, surgery should be undertaken in all cases and an anastomosis between the common venous pool and the waist of the left auricle should be attempted. This should be done under the protection of hypothermia or an extracorporeal circulation. Finally, the common venous drainage to the right auricle should not be ligated at the time of operation because of the additional load thrust on the left heart and the subsequent failure. Whether this common venous channel to the left auricle should be ligated subsequently or not is a decision I would leave to wiser surgeons.

I am indebted to Dr. John Keith and Dr. Richard Rowe, cardiologists at the Hospital for Sick Children, Toronto, for their help in the preparation of this paper and their unfailing interest and enthusiasm.

References

Brown, W. E. (1950). *J. Okla. med. Ass.*, **43**, 98.
Darling and Rothney (1956). Personal communication.
Gardner, F. and Oram, S. (1953). *Brit. Heart J.*, **15**, 305.
Snellen, H. A. and Albers, F. H. (1952). *Circulation (N.Y.)*, **6**, 801.
Whitaker, W. (1954). *Brit. Heart J.*, **16**, 177.

THE OPERATIVE TREATMENT OF THE FUNNEL CHEST*

BY

F. REHBEIN and H.-H. WERNICKE

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The operative correction of the funnel chest is a difficult and important problem. Quite a number of methods and modifications have been mentioned. Late results, however, do not always come up to expectation.

As a seriously deformed funnel chest may lead to troubles of the functions of the lungs and heart (Wegmann and Schaub, 1953; Schaub and Wegmann, 1954) operations should be limited to such cases only. Operating from a cosmetic point of view is not justified. The best age for a child to be operated on is 3 to 5 years. At this age we find an increased tendency to bronchitis, palpitation and delay of general physical development. Very serious disorders of the functions of the lungs and heart become evident in the second decade. On close examination of children under 10 years of age, we often found a reduction in maximum breathing capacity at this age too, as also did Brown and Cook (1951). An abnormal E.C.G. generally due to abnormal location of the heart was observed, too, with patients less than 10 years old. Operating at an early age is primarily a preventive measure.

In many cases surgery has been successfully performed in adults. The operation becomes more difficult because of greater rigidity. The result is mostly not so satisfactory as it would be with a child, but the patient is no longer endangered by growing factors.

The so-called limited, or ligament-cutting operation, at first used by Brown (1939) on infants, is not performed very often. Hausmann (1955) recommends the complete operation as early as the age of 2 years.

Quite irrespective of whatever method may be applied, the operation is divided into two parts: mobilization and stabilization. Methods differ, in particular in the course of stabilization, whereas with regard to mobilization variations to any great extent are not possible.

The substernal ligament or the tough fibrous attachments of the diaphragm and the linea alba to the point of the funnel must be stripped from the ribs to the extent of 2 to 4 cm. each side of the sternum. The sternum is osteotomized in a wedge-like manner at the level of the gladiomanubrial junction. Splitting of the sternum, as recommended by Brunner (1954) and Gross (1953), will, when operating on a child, only be necessary if the sternum itself is shaped like a boat. Handling the costal cartilages varies greatly. Simple incisions, wedge-like or partial resections are recommended. Sauerbruch (1920), Brown (1939), Ochsner and DeBakey (1939) and Therkelsen (1951) have described extensive resections of the three or five lowest cartilages, either removing or preserving the perichondrium.

Though a fibrous stabilization or cartilage regeneration can be expected, it is not desirable to take away the frame from the thoracic wall to a larger extent than necessary. It will be sufficient after elevating the sternum to find out where the cartilage itself is deformed or where too much cartilage is present. Then it is resected step by step until the movable segments can be placed without any tension in the level of the elevated chest wall. In the event of the deformity being of an asymmetrical nature it will be necessary to remove larger segments on the steep side of the funnel.

The anterior chest wall can be fixed in different ways. According to Brown (1939) and Ravitch (1949, 1951, 1952), after completely resecting the cartilages bone suture in the range of wedge osteotomy will be sufficient to hold the sternum in the corrected position. The wire extension at the bottom of the sternum is disadvantageous. The danger of infection is not great but does exist. It may easily happen that too much pulling is caused. Furthermore pulling is only possible within the period of three to four weeks when the chest wall is not quite strong enough. In some cases we have seen new deformity after a good primary result. Once a depression of the sternum was found. In other cases the sternum moved forward out of the

* Presented at the third annual meeting of the British Association of Paediatric Surgeons, London, July 17-19, 1956.

level of the chest wall and to the right and to the left the cartilages developed depressions.

Another way of stabilizing the chest wall is by placing a rib or cartilage under the sternum. This

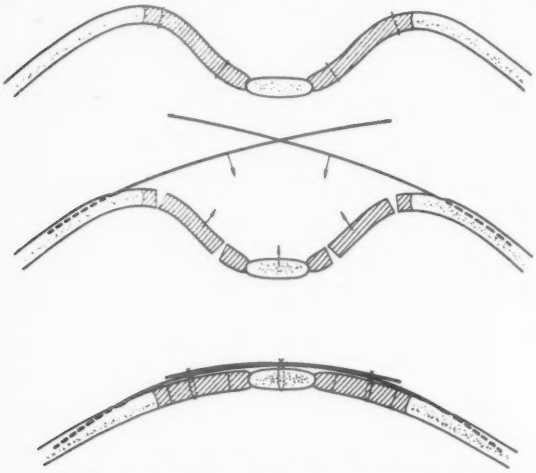
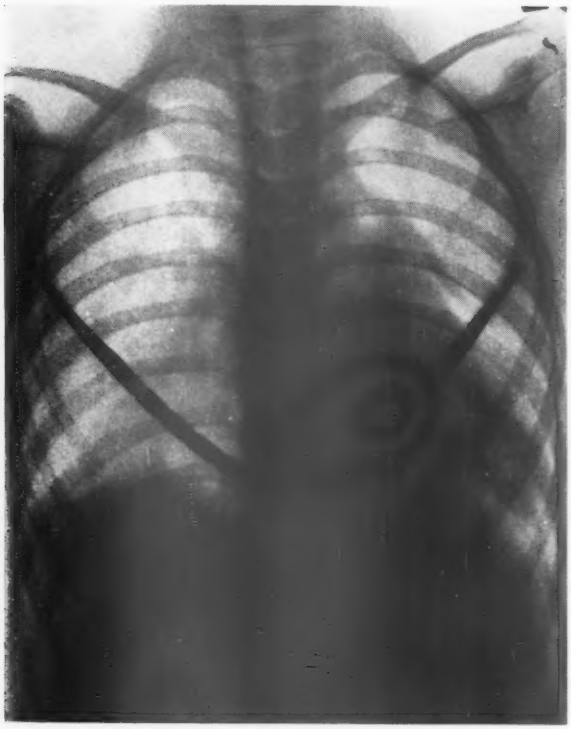


FIG. 1.—Stabilization of the elevated funnel chest with crossed metal blades.

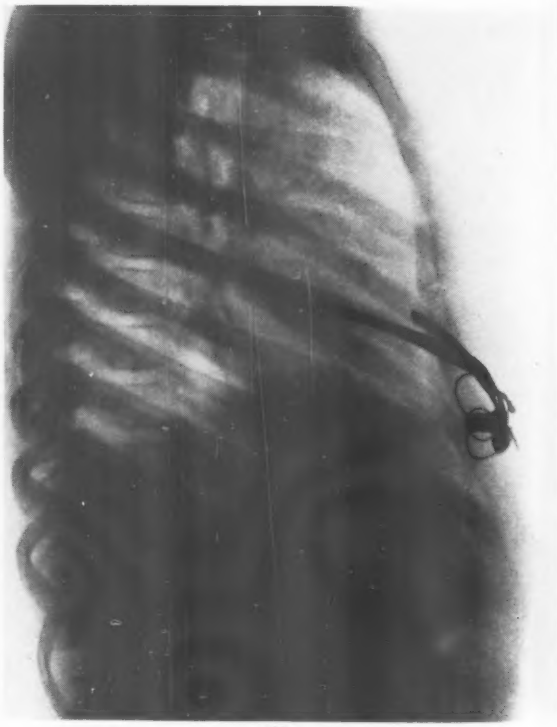
procedure was applied by Dailey (1950), Sweet (1944) and Brodkin (1948). Rotation or removing the sternum is hardly practised today.

During the last 18 months we have applied in 12 cases a different way of stabilizing with children ranging from 4 to 14 years (Rehbein and Wernicke, 1955). After completing the mobilization narrow metal blades were pushed into the rib like a marrow-nail. The sternum and the cartilages are elevated, the blades crossed and depressed. The sternum is fixed with a wire sling at the crossing point elastically. The separate cartilage segments may also be suspended (Fig. 1). Costal cartilages which have been resected before to the necessary extent are now adapted loosely by means of sutures. Deformities of an asymmetrical type with an oblique sternum may be fixed also in this way. Only once was it necessary to split the sternum. The fixation is solid and stable, in particular when the metal blades reach to the other side. The chest wall cannot be depressed. It is suspended like a garland and splinted until completely healed. In operating on slightly deformed funnels one pair of blades will suffice (Fig. 2). In most cases we have used two pairs. In operating on deep funnels of older children three pairs will be necessary (Fig. 3).

As to complications, a pneumothorax on the right side has been noticed several times and can be removed easily by suction. The process of healing was uncomplicated in all cases. After operation the



(*a*)



(*b*)

FIGS. 2*a* and 2*b*.—Radiographs immediately after operation. The corrected sternum is retained with one pair of metal blades.

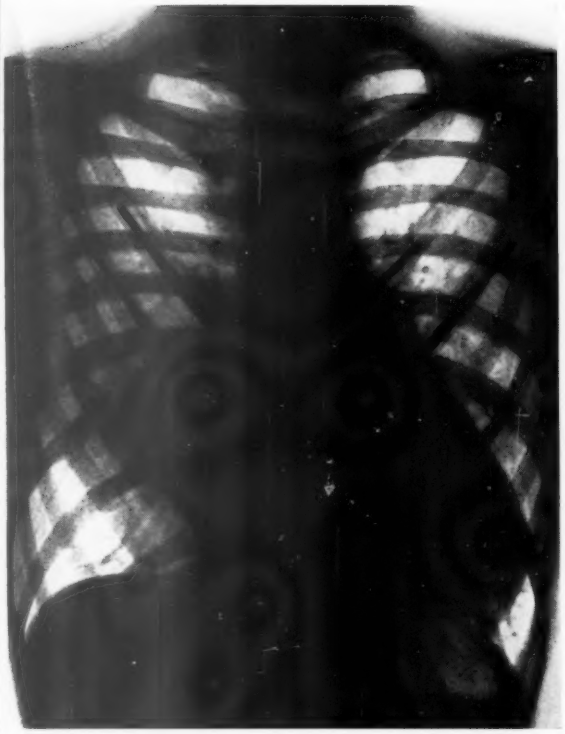
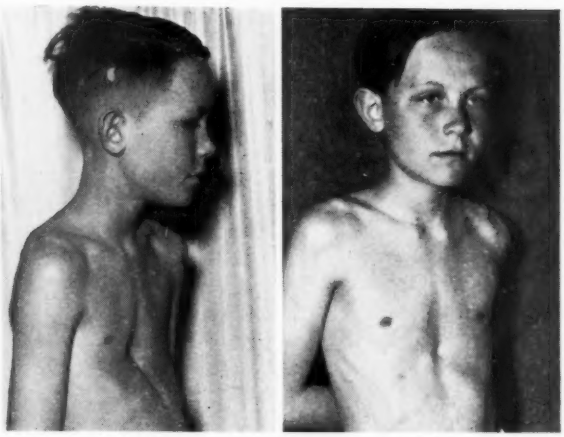


FIG. 3.—Fixation of the corrected anterior chest wall with three pairs of metal blades. Radiograph one year after operation.

children have to lie flat. Only after a few weeks' time are breathing exercises carried through as well as orthopaedic gymnastics, particularly directed to the back.

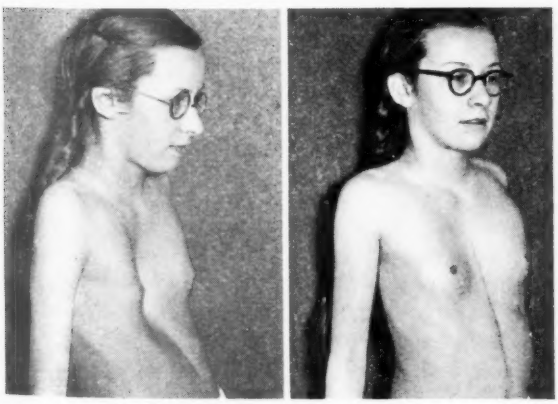
After six months the blades are removed. The result obtained by the operation is unchanged in most cases after the blades have been removed (Figs. 4 and 5). The best results were obtained if there was a deep funnel, the edges of which were not far apart from each other (Fig. 6). If the antero-posterior flattening of the chest is considerable, a correction can only be effected within this particular level. In such a case in spite of splinting a slight depression remained.



(*a*) (*b*)

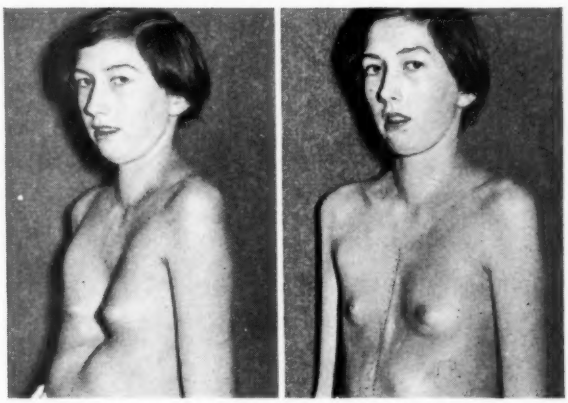
FIG. 5.—Boy, 12 years old, (*a*) before the operation and (*b*) about 12 months after the operation.

The good results obtained without any splinting show that an additional procedure like this is not necessary in all cases. But if there is any uncertainty with regard to stabilization this modification may be a help. The advantage is that the blades may remain for any number of months, at the same time leaving immediately after operation the thorax solid and functioning perfectly. A slight disadvantage is that a second operation will be necessary to remove the blades, but this can be done by a small opening in the scar.



(*a*) (*b*)

FIG. 4.—Girl, 12 years of age, (*a*) before the operation and (*b*) about 12 months after the operation (compare radiograph in Fig. 3.)



(*a*) (*b*)

FIG. 6.—Girl, 14 years of age, (*a*) before the operation and (*b*) after the operation.

REFERENCES

Brodkin, H. A. (1948). *Amer. J. Surg.*, **75**, 716.
Brown, A. L. (1939), *J. thorac. Surg.*, **9**, 164.
—— and Cook, O. (1951). *Dis. Chest.*, **20**, 378.
Brunner, A. (1954). *Chirurg.*, **25**, 303.
Dailey, J. E. (1950). *J. thorac. Surg.*, **19**, 519.
Gross, R. E. (1953). *The Surgery of Infancy and Childhood.* Philadelphia and London.
Hausmann, P. F. (1955). *J. thorac. Surg.*, **29**, 636.
Ochsner, A., and DeBakey, M. (1939). Ibid., **8**, 469.
Ravitch, M. M. (1949). *Ann. Surg.*, **129**, 429.
—— (1951). *Surgery*, **30**, 178.
—— (1952). *J. thorac. Surg.*, **23**, 138.
Rehbein, F., and Wernicke, H.-H. (1955). *Kinderärztl. Prax.*, **23**, 126.
Sauerbruch, F. (1920). *Die Chirurgie der Brustorgane*, Vol. I. Berlin.
Schaub, F., and Wegmann, T. (1954). *Cardiologia (Basel)*, **24**, 39.
Sweet, R. H. (1944). *Ann. Surg.*, **119**, 922.
Therkelsen, F. (1951). *Acta chir. scand.*, **102**, 36.
Wegmann, T., and Schaub, F. (1953). *Schweiz. med. Wschr.*, **83**, 986.

EVENTRATION OF THE DIAPHRAGM*

BY

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This term is accepted as meaning marked elevation of all or part of one hemi-diaphragm due to a congenital aberration in development. Its complex embryonic formation subjects this musculo-fascial structure to areas of potential weakness which is aggravated by the strain of a relative negative pressure in the thorax and the inspiratory muscular pull. Wrong timing, failure of adequate fusion and failures of development lead to weak points and there are therefore opportunities for variation in size and shape as well as for defects.

A congenital hypoplasia with non-development of muscular elements is accepted as its causation leaving the involved diaphragm a mere fibrous sheet or atrophic membrane containing few or no muscular fibres in its peripheral rim. The hemi-diaphragm may function paradoxically if there is also faulty phrenic innervation. The stomach angulates upwards, compressing the lung and displacing the heart and mediastinum, and may cause cardio-respiratory embarrassment. Eventration may be total, which is more frequent on the left, or partial, which is commoner on the right side where the appearance may be mistaken for an accessory liver lobe. It is sometimes associated with arthrogyposis congenita. The incidence is said to be 1 in 10,000 of births.

There may be no symptoms or varying degrees of dyspnoea and cyanosis and these are referable to the cardiovascular, respiratory or digestive systems.

The diagnosis is usually established by radiology revealing an abnormally high position of the affected hemi-diaphragm with a smooth, unbroken arc, and the heart and mediastinum displaced toward the normal side. As diaphragmatic movement is due to varying pressure in the thorax and abdomen as well as the muscle itself, one may see normal motion, but usually fluoroscopy reveals lessened respiratory excursion and occasionally paradoxical movement. Barium studies may help in differentiating the condition from a diaphragmatic hernia where the diaphragm is more difficult to outline and pneumoperitoneal studies may be of value.

Complications, while rare, do occur, and rupture of the thinned-out portion of the diaphragm during labour has been reported. Peptic ulceration, volvulus of the stomach and pneumonia from inadequate pulmonary expansion may occur.

Treatment varies according to the severity of the symptoms and must be as prompt in the newborn with cyanosis and dyspnoea as when caused by a large diaphragmatic hernia. When indicated by cardiovascular or respiratory distress, surgical intervention by the thoracic, abdominal or thoracoabdominal approach is made. The diaphragm is repaired by plication or overlapping with interrupted non-absorbable sutures using tantalum or nylon mesh reinforcement if necessary.

Complete eventration has been repaired in the newborn by suturing the anterior portion of the diaphragm to the circumference of the costal margin of the diaphragm anteriorly, and the posterior portion sewn to the crus medially and renal fascia laterally. The liver in these cases has no peritoneal attachment to the diaphragm and is easily mobilized. If, after replacement, the abdomen is found to be too tense, only the abdominal skin wound is sutured as described by Gross for diaphragmatic hernia.

During the past five years five patients have been admitted to the Royal Alexandra Hospital, Sydney, with a diagnosis of eventration of the diaphragm.

Case Reports

Case 1. N.H., aged 5 days, was admitted to the Royal Alexandra Hospital for Children in 1951 with a history of grunting respirations and repeated cyanotic attacks. After admission the baby's condition remained good, there was no cyanosis or distress and after three weeks' observation he was discharged. The chest radiograph showed the left hemi-diaphragm markedly elevated, with the heart and mediastinum displaced to the right. The left dome moved evenly with the right. He has remained well since. A chest radiograph in 1955, when he was still symptom-free, showed marked elevation of the left hemi-diaphragm with the heart and mediastinum still displaced to the right side.

Case 2. K.B. was admitted in 1954 aged 3 weeks, with a history of cyanosis except when oxygen was administered and rapid respirations. A caesarean operation had

* A paper read at the meeting of the British Association of Paediatric Surgeons in London in July 1956.

been performed on account of a shoulder presentation. After admission, the baby appeared to be in no distress. A chest radiograph revealed an elevated right hemi-diaphragm which moved paradoxically suggesting phrenic paralysis. A barium study showed the distal end of the stomach much higher than the cardia due to elevation of the liver. This baby was discharged after two weeks in hospital and has remained symptom free since.

Case 3. D.F., aged 6 years, was admitted in 1953 with a history of chronic cough and recurring attacks of vomiting since birth. A chest radiograph showed the anterior two-thirds of the left hemi-diaphragm elevated and this portion exhibited paradoxical movement. The posterior third was normally attached and contracted normally with the right side. The heart was displaced to the right, and the stomach rotated anti-clockwise. There was scoliosis convex to the left. A thoracotomy operation was performed and the redundant portion of the thin fibrous central portion of the diaphragm excised with suture of the muscular margins. Histologically the tissue examined consisted entirely of compact acellular bands of collagen and was devoid of any striated muscle. This girl continued to vomit, especially after lying down at night, and a subsequent chest radiography showed a similar bulge of the left hemi-diaphragm. Thoracotomy was repeated later and the defect closed by a fascia lata reinforcement. She has been well since.

Case 4. J.H., aged 7 years, was operated upon two years ago for repeated episodes of bronchitis, with a chest radiograph showing a large eventration in the left hemi-diaphragm. At thoracotomy the central membranous area of the diaphragm was excised, sutured at the margins and reinforced. Histologically the specimen consisted of collagen tissue with no striated muscle. He has been well since.

Case 5. A man, aged 48 years, complained of pain in the left chest for 2 months aggravated by coughing, and vomiting and dyspnoea for 4 days. There was no history of trauma or any earlier relevant symptoms. He is a zoo attendant and says he has to do heavy lifting at times. On admission to hospital, he was ill, dyspnoeic and distressed. There was no movement in the left chest, which showed signs of pleural effusion. A chest radiograph reported an eventration of the diaphragm with mediastinal shift and a large amount of stomach in the left chest. A barium swallow showed marked elevation of the left diaphragm with paradoxical movement and volvulus of the stomach. Great relief was obtained by gastric suction, and at a subsequent operation a 3 in. rent was found in a thinned central portion of the left diaphragm through which stomach, spleen and splenic colon had entered. These organs were reduced and the rent plicated securely. Convalescence and subsequent progress was uneventful. This appears to be a rare case of rupture of a partial eventration on the left side. Mr. Norman Tanner said recently that he had encountered five or six cases since 1943 of volvulus of the stomach in adults secondary to eventration of the diaphragm. He merely ligates the gastro-colic omentum and allows the colon to go up into the chest and places a few anchoring sutures in the stomach bed.

Case 6. A baby aged 3 months was admitted on account of frequent vomiting and cyanotic attacks but died soon after admission to hospital. The necropsy revealed faulty development of the diaphragm on each side so that the central portions were formed of membrane only, while the muscle arched anteriorly and posteriorly around the area of muscular deficiency. On the right side the right lobe of the liver projected into and occupied one half of the pleural cavity. On the left side the spleen and distended stomach projected upwards similarly. None of the viscera were within the pleural sac as the membranous diaphragm enclosed them above. The lungs were malformed and collapsed and directly related to the misplaced abdominal viscera. The liver was misshaped and deeply grooved.

Summary

A résumé of eventration of the diaphragm is given.

Case histories of five infants and one adult with rupture are described.

OESOPHAGEAL RECONSTRUCTION IN CHILDREN USING INTRATHORACIC COLON*

BY

CHARLES D. SHERMAN, JR. and DAVID WATERSTON

From The Hospital for Sick Children, Great Ormond Street, London

This paper records our experience in the use of colon for oesophageal reconstruction in children, and includes a summary by one of us of similar cases operated on in other centres.

In 1894 Bircher reconstructed the oesophagus using a subcutaneous skin tube. Since then many methods of reconstruction have been tried both clinically and experimentally; these methods have included the use of stomach, skin tubes, jejunum, colon, aorta, inert tubes, etc. The early work has been well summarized by Ochsner and Owens (1934) and the more recent work by Mahoney and Sherman (1954).

Sandblom (1948) was the first to use the colon for reconstruction in atresia of the oesophagus, and it was his work that stimulated one of us (D.J.W.) to attempt this method using a slightly different technique. Lundblad (1921) had previously used the colon for reconstructing the oesophagus in a 3-year-old child suffering from a corrosive stricture. He also showed (1934) that such an oesophagus grew with the child and functioned satisfactorily 15 years after operation.

Indications for Reconstruction of Oesophagus

Atresia of Oesophagus without Tracheo-oesophageal Fistula. In our experience this type of deformity is always associated with a very wide gap between the blind ends of the oesophagus; the lower segment is rarely more than 1 cm. in length. In these cases also, the stomach and intestines are extremely small; the child has been unable to swallow liquor amnii before birth and the intestinal tract has therefore not developed adequately. Both these facts, i.e., the wide gap and the smallness of stomach and intestines, make a primary anastomosis impracticable.

We feel that it is unwise to bring the stomach up to the apex of the chest in the newborn, and that in these cases no primary anastomosis should be attempted. The upper oesophagus should be brought out on the left side of the neck for drainage of saliva and a gastrostomy made for feeding. The subsequent reconstruction of the oeosophagus should be delayed until the baby is thriving and gaining weight.

As the absence of gas below the diaphragm does not rule out the presence of a tracheo-oesophageal fistula (Waterston, 1954), it follows that these cases should have an exploratory right thoracotomy as a preliminary to the oesophagostomy and gastrostomy.

Atresia of Oesophagus with Tracheo-oesophageal Fistula. Unquestionably the treatment of choice in these cases is a primary anastomosis, and we feel that with careful freeing of the upper and lower segments of oesophagus a tension-free anastomosis can be obtained in over 90 % of such cases. However, if the distance between the ends of the oesophagus is great and there is any doubt about the soundness of the suture line, then an oesophagostomy and gastrostomy should be done after the fistula and lower segment of the oesophagus have been tied off in the chest.

Reconstruction can then be carried out when the baby is in good general condition.

Stricture of the Oesophagus. Severe stricture affecting the long segment of the oesophagus, whether caused by the swallowing of corrosives, or by the acid reflux from an incompetent cardia, may sometimes necessitate wide resection. If a primary anastomosis is not feasible, then reconstruction with colon is an attractive method of reconstruction.

Miscellaneous Conditions. There is a growing feeling among surgeons that the oesophagus should almost never be anastomosed to the stomach for any condition. In a child whose oesophageo-gastric junction has been resected (for example, for bleeding varicosities) it is felt that interposition of a loop of colon between the lower oesophagus and stomach is a preferable method to anastomosis of oesophagus

*A paper read at the meeting of the British Association of Paediatric Surgeons in London in July, 1956.

TABLE
COLON TRANSPLANTS IN CHILDREN

	Case	Condition	Colon	Route	Follow-up
*†Battersby (Indianapolis)	1	Atresia	Right	Retrosternal	3 years. Eats everything
	2	,,	,,	R. posterior chest	Died 3 weeks post-operatively. ? cause
	3	Stricture	,,	,, ,,	
	4	,,	,,	,, ,,	
	5	,,	,,	,, ,,	All have survived
	6	,,	,,	,, ,,	
	7	,,	,,	,, ,,	Developed marginal ulcer and perforated
†Gross (Boston)	8	Atresia	Left	Left posterior chest	
	9	,,	Right	,, ,,	
	10	,,	,,	,, ,,	Three late deaths of ? cause with bowel necrosis
	11	,,	,,	,, ,,	3 cervical fistulae. All healed spontaneously
	12	,,	,,	Retrosternal	2 patients living not longer than 1½ years follow-up
†Haight and DeWeese (Ann Arbor)	13	,,	,,	,,	1 death secondary to pulmonary complications (13). Fistulae in neck in 2 (13 and 14). Follow-up less than 6 months
	14	,,	,,	,,	
	15	Stricture	,,	,,	
*†Jewett (Buffalo)	16	,,	,,	,,	Small bowel obstruction (adhesions) at 6 weeks relieved by operation, follow-up 2 months
†Koop (Philadelphia)	17	Atresia	,,	,,	Appendiceal stump used for 1 anatomosis and patients died. Cases 18 and 19 live and well 1-2 years
	18	,,	,,	,,	
	19	,,	,,	,,	
*†Nadal (Portland)	20	TE fistula	,,	,,	Follow-up 1 year. No complications
†Rickham (Liverpool)	21	Atresia	Left	Left posterior chest	Died of ? damage to blood supply by diaphragmatic hernia
*Sherman and Dale (Rochester)	22	,,	Right	Retrosternal	Live and well 2½ years. Mild stasis post-operatively
	23	TE fistula	,,	,,	Cervical fistula with stenosis requiring revision. Alive and well 2½ years
*Waterston (London)	24	Atresia	Left	Left pleural cavity	
	25	,,	,,	,, ,,	1 death, others alive and well. Distal anastamosis to oesophagus above diaphragm
	26	,,	,,	,, ,,	
	27	,,	,,	,, ,,	
		Other non-malignant cases (including adult strictures)			
†Campbell (Geneva, N.Y.)	28	Stricture	Right	Retrosternal	Cervical fistula at 12 days, alive and well at 3 months
*†Day (Jacksonville)	29	,,	,,	,,	Colon mobilized at 1st stage. Extensive adhesions at 2nd and patient died ? secondary to prolonged surgery
*†Grant (New York)	30	,,	,,	,,	Died at 7 weeks. Mediastinal abscess. Pulmonary complications
Kergin (Toronto)	31	Paraffinoma	Transverse	Postero mediastinal	Alive and well at 3 years
†Koop (Philadelphia)	32	Bleeding varices	Oesophago-gastrectomy with interposition of transverse colon		2 patients moribund before surgery, died.
	33	,, ,,			3rd case alive and well at 4-5 months
	34	,, ,,	,,	,, ,,	
†Clatworthy (Cleveland)	35	,, ,,	,,	,, ,,	?

* To be published. † Personal communication.

to stomach. Although not utilized by us, this procedure has been performed recently by other surgeons in patients who have continued to bleed from oesophageal varices despite various shunting procedures (Table).

Two Methods of Reconstruction

We describe two methods of reconstruction. The first (devised by Waterston) is reconstruction with transverse colon transplanted iso-peristaltically into the left posterior chest on a pedicle containing the left colic artery. This method has been used by one of us (D.W.) in four cases, and the first baby was operated on on September 22, 1951. Figs. 1-5 show diagrammatically the stages of the procedure as applied to a case of atresia of the oesophagus without tracheo-oesophageal fistula.

This method has the advantage of preserving intact the all-important cardiac sphincter mechanism between the oesophagus and stomach.

J.P. was born on December 11, 1952, of healthy parents. His mother was a midwife and had been taught that hydramnios in the mother was not infrequent in cases of oesophageal atresia. As she had hydramnios she persuaded her obstetrician to pass a stomach tube on the baby immediately after birth (Waterston, 1955). She was right (Fig. 7). No gas below the diaphragm suggested, but did not rule out, the absence of tracheo-oesophageal fistula.

At the first operation on December 12, 1952 (by D.W., anaesthetist Dr. B. G. B. Lucas), using endotracheal oxygen with a relaxant, a right axillary thoracotomy through the fourth interspace was done. The blind end of the upper oesophagus was freed and the end marked with a black stitch. The absence of a tracheo-oesophageal fistula was confirmed. The lower oesophagus consisted of a small blind pouch extending for 1 cm. above the diaphragm. The distance between the two ends of the oesophagus was more than 10 cm. The thoracotomy wound was closed in layers. A high gastrostomy was done through the linea alba using the smallest Malecot self-retaining catheter.

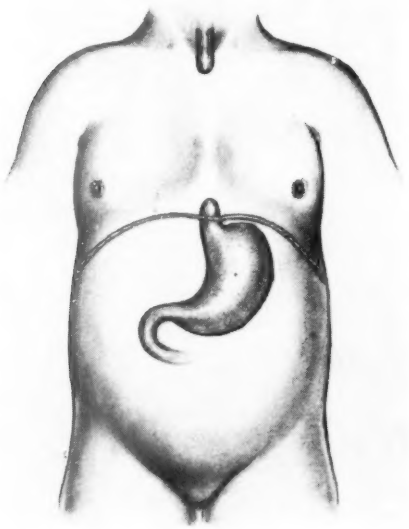

FIG. 1.

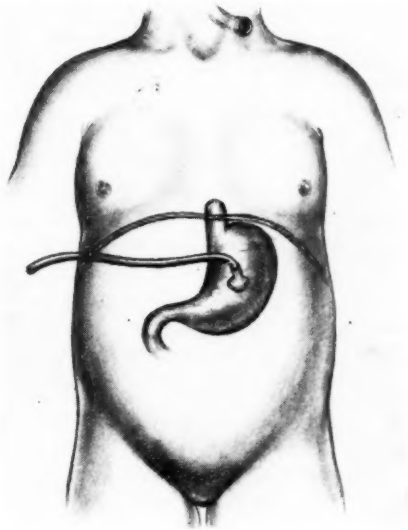

FIG. 2.

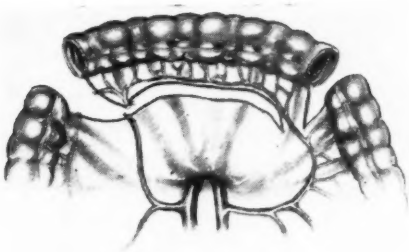

FIG. 3.

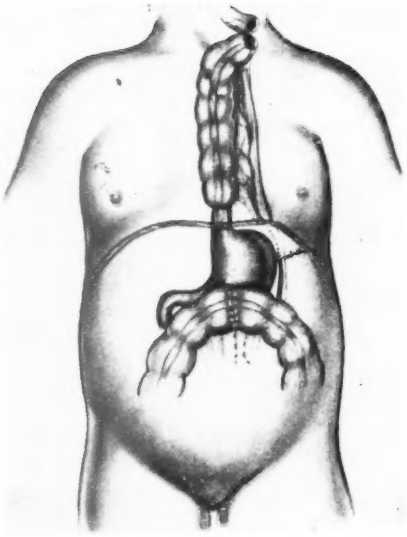

FIG. 4.

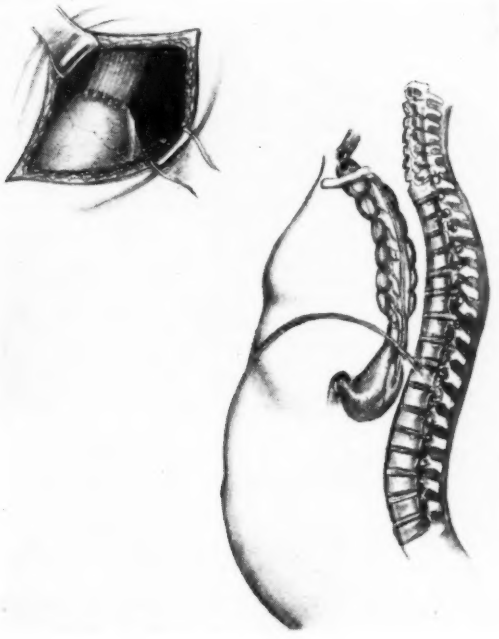

FIG. 5.

Through a transverse incision 4 cm. in length above the left clavicle and dividing part of the clavicular head of the sternomastoid, the upper pouch of oesophagus was brought out from the upper mediastinum; it was opened at the terminal marking stitch and its edges stitched to the skin with interrupted silk.

Post-operatively, the baby was fed by gastrostomy, oral feeds being also given which drained through the oesophagostomy.

The second operation (D.W.) on June 7, 1953 (anaesthetist Dr. B. G. B. Lucas), endotracheal oxygen and ether with relaxant were used.

Through a transverse abdominal incision the transverse colon was isolated on a pedicle containing the left colic artery. The middle colic artery was divided close to its origin. Continuity of the colon was re-established by end-to-end anastomosis using one layer of interrupted 0000 silk.

The proximal end of the isolated transverse colon was closed and attached by a nylon stitch to the skin at the right end of the skin incision. The wound was then closed in layers leaving the distal opening of the transverse colon as a colostomy at the left end of the skin incision.

Post-operatively the isolated loop of transverse colon was irrigated through the colostomy with a solution containing streptomycin and sulphasuxidine.

The third operation was performed eight days later. The anaesthetic was again endotracheal oxygen and ether with a relaxant.

With the baby on the right side the previous transverse abdominal incision was extended laterally through the tenth interspace into the chest. The diaphragm was incised towards but not into the oesophageal hiatus; the spleen was removed. The marking stitch attaching the colon to the abdominal wall was divided and the isolated loop of transverse colon brought up into the left chest. The pedicle containing the left colic artery lay without tension, and there was adequate length of colon to reach up to the neck.

An incision was made just below the cervical oesophagostomy and the apex of the pleura opened by blunt dissection; the proximal end of the transverse colon was then brought out to the skin of the neck.

The distal stump of oesophagus was then freed and an end-to-end anastomosis made between it and the distal end of the colonic loop, using a single layer of 0000 interrupted silk.

The incision in the diaphragm was then closed with interrupted linen thread, care being taken not to close it too tightly round the pedicle containing the left colic artery. The thoraco-abdominal wound was then closed in layers.

Feeding was continued by gastrostomy.

The fourth operation was performed on August 24, 1953. Under general anaesthesia an end-to-end anastomosis was carried out between the oesophagostomy and the colonic loop in the neck; the skin was closed over the anastomosis (Fig. 4A).

Oral feeding, which had been kept up since birth, was started again two days after the fourth operation; the baby was very soon able to take his full feeds by mouth and thereafter gastrostomy feeds were withdrawn. The gastrostomy wound closed spontaneously after withdrawal of the gastrostomy tube, apart from a very small gastric fistula which leaked occasionally. This was closed by oversewing it on August 20, 1955.

The baby remained very well until September 20, when part of the stomach which had herniated through the incision in the diaphragm underwent torsion in the left chest and became acutely distended. He became rapidly shocked with complete collapse of the left lung and displacement of the mediastinum to the right.

The tension within the chest was relieved by re-opening his gastrostomy, with a dramatic improvement in his general condition.

On October 15 the diaphragmatic hernia was repaired and the diaphragm stitched more carefully round the pedicle containing the left colic artery. Since then he has continued to thrive and develop normally. He eats everything and has no difficulty at all with swallowing. He eats his meals as quickly and with as much enjoyment as other children.

The radiographic appearances on barium swallow show the reconstructed oesophagus to function well; the segment of transverse colon shows peristalsis of the colonic type, i.e., the meal is pushed on by a 'mass movement' type of peristalsis. It empties itself rapidly into the stomach; the cardiac sphincter is competent and no reflux can be elicited.

Two other babies have been operated on by this technique. They are now 4 and 5 years old and both are thriving and swallowing normally.

A fourth case was operated on in 1954; an attempt was made to combine stages 2 and 3 into one operation. The colonic loop was pulled up too tightly into the neck, thereby 'bowstringing' the artery of supply. The colonic loop became gangrenous and the child succumbed a few hours after operation.

The second method of reconstruction uses right colon transplanted isoperistaltically in the retrosternal position (Charles D. Sherman, Jr.). At the initial emergency procedure in infants with oesophageal atresia of tracheo-oesophageal fistula, it is felt wise to delay reconstruction; the cervical oesophagus is brought out in the left neck and a gastrostomy is done the following day. At a later date, varying from a few weeks to a number of months depending on the patient's condition, oesophageal reconstruction is performed. Preoperative bowel preparation consists chiefly in the administration of neomycin and sulphathalidine to prepare the lower ileum and colon for section. At operation a longitudinal incision extending to the xiphoid is utilized and the right colon mobilized by cutting the lateral attachments. The length of the right colon is estimated and the collateral vascular supply evaluated by placing a bull-dog clamp on the ileo-colic artery. During the waiting period to ascertain whether the blood supply to the caecum is

maintained, appendectomy is done by the routine manner. The ileum is sectioned approximately 4-6 in. proximal to the ileo-caecal valve. This leaves a long segment of ileum which can be utilized and anastomosed to the cervical oesophagus if it proves to be necessary to gain adequate length. The transverse colon just to the left of the middle colic artery, taking care to avoid injury to the marginal vessel, is sectioned and after sectioning the ileo-colic vessels the entire transplant can be swung to the neck. The blood supply to the entire transplant then comes through the middle colic vessels. The transplant is carried through the substernal tunnel which is cleared by blunt dissection immediately beneath the sternum in the anterior mediastinum. The reconstruction is terminated by end-to-end anastomosis of the caecum or ileum to the cervical oesophagus, by anastomosis of the lower end of the transplant into the anterior wall of the stomach, and by end-to-end ileo-transverse colostomy. The wound is closed with interrupted fine silk sutures. The gastrostomy is left in place and may heal spontaneously, or may be closed at a later date. Pneumothorax sometimes occurs during the operative dissection and is handled by simple needle aspiration at the end of the procedure. The procedure is illustrated (Fig. 6).

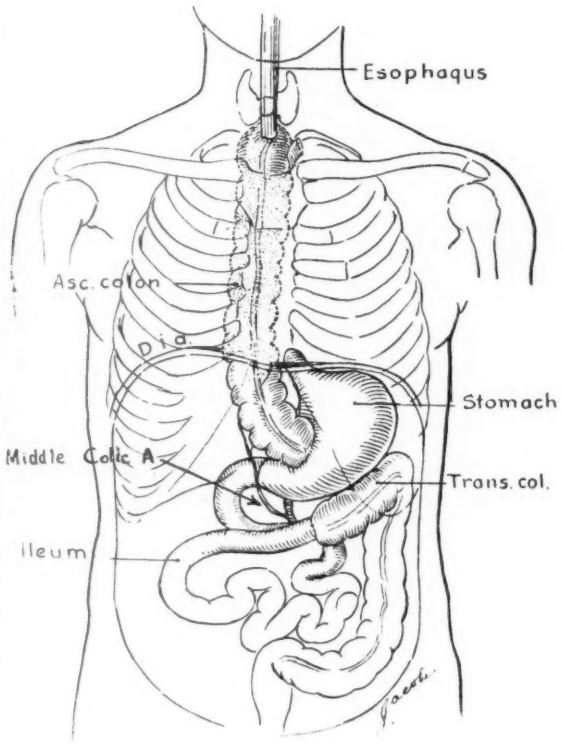

FIG. 6.

Other Methods of Transplantation

Studies of the colonic blood supply have shown that infrequently one or other of the above methods may be impracticable because of lack of collateral circulation. Should this be true it is imperative that surgeons be acquainted with other possibilities. These include (1) utilization of the transverse colon with the blood supply based upon the middle colic and right superior colic vessels; (2) utilization of transverse colon with the blood supply based upon the middle colic artery and left superior colic artery; (3) utilization of the descending colon with the blood supply based upon the middle colic artery; (4) utilization of caecum and terminal ileum with the blood supply based upon the ileo-colic artery; and (5) various methods of utilization of the jejunum and stomach.

Discussion

The type of reconstruction used by Waterston and others has the advantage of preserving the normal oesophago-gastric junction. Since the colon is not anastomosed to the stomach there is no danger of later peptic digestion of the colon and perforation. Although Sherman feels that this is a relatively unusual complication, it has occurred in at least one case. This reconstruction leaves the patient with the least disturbance to normal physiology. The main disadvantage to this procedure is the fact that the blood supply must be brought through the diaphragm and considerable care must be taken to make sure that the opening in the diaphragm is neither so large as to result in a hernia, nor so small that it causes vascular obstruction. There have been some post-operative problems with herniation through the diaphragmatic opening and this may account for vascular obstruction with subsequent necrosis of the colonic transplant and death of the patient (Table). Sherman feels that there will be a larger percentage of patients who have inadequate collateral circulation to nourish the transplant when dependance is placed upon the inferior colic artery to carry blood all the way to the mid-transverse colon.

The advantage of the right colon transplant as utilized by Sherman and others lies in the fact that the anterior mediastinal route seems a very satisfactory one because it is the shortest distance to the neck and because it does not interfere with the blood supply to the transplant. A disadvantage as compared with Waterston's method seems to lie in the possibility of peptic ulceration of the lower end of the colon where it is anastomosed into the stomach. Although it is felt that the colon is much more resistant to peptic digestion than is the oesophagus or jejunum, it must be admitted that at least one case has had colonic erosion with perforation (Table).

Although the right colon transplants have been done in one stage, as contrasted with three stages for the transverse colon transplant as done by Waterston, at least one patient has required a subsequent minor operation for revision of a stenosis at the cervical anastomosis.

The question whether the cervical anastomosis should be done at the initial reconstruction or the second stage is a matter of opinion. Sherman feels that this anastomosis should be done at the initial reconstruction thereby saving a certain number of patients a later reconstruction. Should the initial anastomosis break down his experience would indicate that these cervical fistulae will heal spontaneously and will rarely necessitate secondary reconstruction. Waterston, on the other hand, feels that it is safer to delay the cervical anastomosis for a subsequent stage.

Will the use of colon transplantation decrease the mortality in tracheo-oesophageal fistula and atresia? The current mortality rate around the world in patients with tracheo-oesophageal fistula and atresia varies tremendously from somewhere around 20 % to approximately 80 %, depending upon the area and the type of medical centre where these patients are handled. Associated congenital anomalies also cause some mortality. A large proportion stems from the fact that these patients are frequently in very poor condition when seen initially by the surgeon. However, at least some of this mortality is caused by (1) the surgeon's compulsion to do a primary anastomosis even though it looks as though it might break down subsequently; and (2) the added operating time in a poor risk patient entailed by mobilization of the stomach and various other methods of performing a difficult anastomosis. It may be that by avoiding these two factors one can decrease the mortality rate. In these difficult cases we believe that delaying reconstruction and subsequent repair with a colon transplant will yield an overall case mortality rate much lower than will be attained by going ahead with emergency initial reconstruction.

What is the significance of colonic peristalsis to these transplants? Limited experience suggests that an isoperistaltic transplant works better than an antiperistaltic transplant. This is certainly true using small bowel which maintains a considerably more active peristalsis than does the colon. We do not believe that this question has been definitely settled, however. It is certain that colonic peristalsis is very slow and that it probably plays very little part in propelling the food from the mouth to the stomach. Both Harrison (1949) and Syring (1914) have reported difficulty in cases in which antiperistaltic small bowel loops were used. However, the left colon has been used in an antiperistaltic manner in a number of cases with apparently little difficulty (Lundblad, 1921; Waterston, 1955; Toupet, 1951). Further experimental work and further clinical evaluation on this point are needed.

What can be done to decrease the incidence of cervical fistulae? Although this has not been a serious clinical problem, it has remained a troublesome complication even when the anastomosis has been done by so experienced a surgeon as Gross (Table). Sherman has tried wrapping the anastomosis (in an adult) with a free graft of peritoneum, but this patient developed a cervical fistula. The utilization of small bowel rather than caecum for the anastomosis has not seemed to make any significant difference as to whether a fistula develops. If this continues to be a troublesome complication, it may be advisable to use catgut entirely for the anastomosis in order to prevent splitting silk for a prolonged period of time. Waterston feels that it is probably better to delay the cervical anastomosis for a subsequent minor operation than to risk fistula and subsequent stenosis. The incidence of fistula formation seems lower when the cervical anastomosis is delayed.

Concern about the blood supply to a transplant arises when utilizing right colon as described by Sherman. In an occasional patient the middle colic artery has seemed to be tight when placed anterior to the pylorus. In those cases it is certainly safer to bring the entire transport and blood supply posterior to the stomach thereby eliminating the possibility of obstruction in the pyloric area.

Conclusion

Although reconstruction of the oesophagus by colon transplant is still in the developmental stage, sufficient experience has been accumulated to suggest that further trial and evaluation are worth while. Several years of further observation of these patients will be necessary before we can with certainty justify our initial enthusiasm for the use of this procedure.

References

Battersby, J. S. (1953). *Surg. Forum*, **4**, 279.
Dale, W. A. and Sherman, C. D., Jr. (1955). *J. thorac. Surg.*, **29**, 344.
Goligher, J. C. and Robin, I. G. (1954). *Brit. J. Surg.*, **42**, 283.
Harrison, A. W. (1949). *J. thorac. Surg.*, **18**, 316.
Kelling, G. (1911). *Zbl. Chir.*, **38**, 1209.
Lundblad, O. (1921). *Acta chir. scand.*, **53**, 535.
—— (1934). *Ibid.*, **75**, 73.
Mahoney, E. B. and Sherman, C. D., Jr. (1954). *Surgery*, **35**, 937.
Ochsner, A. and Owens, N. (1934). *Ann. Surg.*, **100**, 1055.
Orsoni, P. and Toupet, A. (1950). *Presse méd.*, **58**, 804.
Sandblom, P. (1948). *Acta chir. scand.*, **97**, 25.
Sherman, C. D., Jr., Mahoney, E. B., Dale, W. A. and Stabins, S. J. (1955). *Cancer*, **8**, 1198.
Syring, —. (1914). *Dtsch. Z. Chir.*, **128**, 260. Quoted by Ochsner and Owens.
Toupet, A. (1951). *Rev. Chir. (Paris)*, **70**, 70.
Waterston, D. J. (1954). In *Recent Advances in Paediatrics*, ed. Gairdner, D. London.
—— (1955). In *Modern Trends in Obstetrics and Gynaecology (Second Series)*, ed. Bowes, K., p. 294. London.

ABNORMALITIES IN MECONIUM OF THE FOETUS AND NEWBORN*

BY

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Aristotle apparently was the first to give the name 'meconium' to the intestinal contents of the foetus. The word 'mecon-arion' means 'from poppy', or 'like opium', suggesting that the ancients believed it to be the substance maintaining the foetus asleep in the uterus!

Meconium has interested people for a long time (Davy, 1844; Hymanson and Kahn, 1919), but it is only recently when serologists have sought blood group substances in the mucopolysaccharides of meconium that it has been subjected to serious chemical study. Meconium is a large mass of mucus consisting basically of water, muco-proteins and mucopolysaccharides (Rapoport and Buchanan, 1950; Buchanan and Rapoport, 1952). This gives it its general physical properties which are more allied to that of plastic substances than to true simple or colloidal solutions. Biliverdin gives meconium its green colour. There are a number of chemical constituents: fats, steroids, urea, enzymes and sugars (Feldman, 1920). In addition it contains 'meconium bodies', light yellow masses, and organized material in the form of keratinized and nucleated squames.

The purpose of this paper is to draw attention to some changes in the physical properties of meconium apart from meconium ileus, which are of clinical importance. The clinical aspects of many of the cases from which the material for this study was made are described by Zachary (1957) in the next article.

Keratinized and Nucleated Squames and Lanugo Hairs

Lanugo hairs are usually so scanty as to be of no importance. Nucleated squames and epithelial cells usually occur in small numbers and in the upper small bowel chiefly. We have seen no large masses of such cells.

Normal meconium contains a very variable number of keratinized epithelial squames (Emery, 1952) which are apparently derived from the infant's skin, ingested by way of the amniotic fluid and passed through the whole length of the child's intestine.

This constituent has been used in 'Farber's test' (Farber, 1933) as a means of verifying the patency of the infant's intestinal tract. The squames are usually fairly evenly dispersed in the meconium, but not infrequently are seen in sections to be in dense whirled masses; such masses are usually somewhat paler to the naked eye than the surrounding meconium. Digonnet and Fèvre (1943) consider that these epithelial masses may cause obstruction, but these whirls have never, in our experience, been large enough or firm enough to cause any gross intestinal disturbance. On the other hand we have seen such masses apparently obstructing small air vessels in the lung.

Ano-Rectal Plugs

Meconium is usually uniformly bile-stained and a deep green, but in infants with any type of obstruction masses of white mucus are common, particularly in the large bowel. The small masses of 'rabbit dropping' stools of small bowel atresia are usually covered with white mucus.

The terminal mass of meconium in the rectum and anus has a pale, unpigmented cap. This, the '*mekonium pfropf*' of German writers (Cramer, 1900; Weil, 1902), was apparently first described by Ceranus of Ephesus, and is also mentioned by Aristotle (Mardner, 1909). As Weil (1902) pointed out, the '*mekonium pfropf*' does not contain lanugo hairs and keratinized epithelial cells, i.e., it appears to be entirely of intestinal origin. The ano-rectal plug was formerly thought to be of medico-legal importance in the diagnosis of live and still birth, but Cramer (1900) found that in a series of 50 normal infants, 31 had passed this meconium plug before birth. He considered that the plug arose from that

* A paper read at the meeting of the British Association of Paediatric Surgeons in London in July, 1956.

part of the intestinal tract, normally the colon and rectum, in which bile is not secreted.

One of the earliest reported cases of intestinal obstruction (Berti, 1898) was found plugged by a 'meconium worm', thought to be produced by inflammatory change. Falls and Jaffe (1931) in a survey found ano-rectal plugs in approximately 1 % of all newborn babies, and they considered that in one-fifth of these, i.e., one in 500 infants, this plug caused persistent obstruction, leading to death.

This terminal ano-rectal plug differs from the rest of the meconium, in that it is frequently firmer, and, after fixation in formalin becomes hard, apparently due to its relatively high protein content, and similar to the meconium of meconium ileus. In the uterus, peristaltic action appears to occur in the small intestine, but the expulsive action of the rectum and anus is completely inactive. The ano-rectal plugs are certainly related to difficulty in the commencement of bowel action in the newborn, but it is not certain whether the plugs themselves cause the difficulty, or if in such cases there is a delay in the starting of the expulsive action of the large bowel and rectum. Fleury (1952) considers that these cases can respond to prostigmine.

Fig. 1 illustrates an anal meconium plug passed by an infant aged 2 days, and Fig. 2 a plug *in situ* from a child who died with intestinal obstruction and in whom no anatomical cause of obstruction was found.

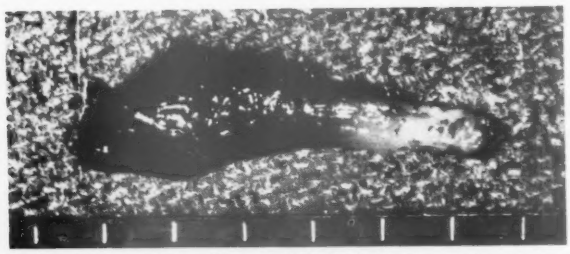

FIG. 1.—Ano-rectal plug from a child who had not passed meconium for two days after birth. This is an ano-rectal plug indistinguishable from a normal plug, the pale end being that adjacent to the anus.

FIG. 2.—Ano-rectal plug from a child dying with intestinal obstruction. The pancreas in this child was completely normal, and no other cause for the intestinal obstruction was found, other than this mass in the colon and rectum.

Meconium Plugs Elsewhere in the Intestine

An occasional finding at routine necropsy on s ill-born infants is a segment of partial obstruction in the intestine. In a series of approximately 800 s ich necropsies we have seen three in the small intes ine and one in the large intestine. The obstruc ion appears to be due to a segment of firm tenacious meconium, forming the tip of a cone at the obstructing point. Fig. 3 shows the external appearance of an obstructed segment in the small intestine. Opened,

FIG. 3.—Segment of small intestine from a child dying during delivery. The tenacious plug of meconium is in the rapidly narrowing segment adjacent to the area of widest diameter.

this bowel contained normally pigmented meconium, that at the proximal end being thin and fluid as normal meconium. The tryptic activity of the meconium was the same and normal at both the obstructing and the proximal end. The viscidity of the end plug as measured by the surface tension method showed a viscidity as high or higher than that found in meconium ileus. The water content of this obstructing plug was extremely low (57 %, normal 75-85 %). Fig. 4 shows the water and surface tension findings in this case, and the marked inverse relationship between the water content and viscidity of meconium

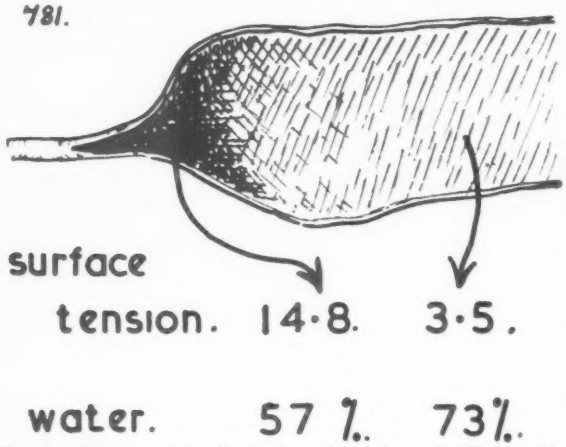

FIG. 4.—Diagram of the dissected specimen shown in Fig. 3, giving the surface tension measurements of the meconium and the water content as taken from the inspissated plug and the relatively normal meconium adjacent.

that occurs even in normal meconium (Emery, 1954).

The pancreas in these cases appeared to be completely normal and no abnormality could be found in the intestinal neural plexus. We have not seen a death due to this type of meconium plug at necropsy, but from the clinical histories of some children (Zachary, 1957, case 3) in whom there was temporary intestinal obstruction after normal meconium had been passed, it seems likely that such plugs had been present and active. In two of the cases seen by Falls and Jaffe (1931) there had been a similar history of children previously passing normal meconium before passing an inspissated plug. The cases reported by Ullmann (1894) seem to have been of the same nature.

Burger (1938) reported a child with intestinal obstruction due to a solid mass of meconium in the lower ileum. In this case, the pancreas showed only exaggerated lobulation. He thought that the tenacity of the meconium may have been due to abnormal resorption of fluid. He refers to two other similar cases that have been reported elsewhere.

The interest of these meconium plugs also lies in their possible connexion with intra-uterine intestinal obstruction and meconium peritonitis (Simpson, 1838; Thelander, 1939; Low, Cooper and Cosby, 1949; Franklin and Hosford, 1952), and also with the cases of what are at first suspected to be meconium ileus, but show none of the other features of the fibrocystic syndrome (Farber, 1944; Shwachman, Pryles and Gross, 1956).

Meconium Bodies

Within the green fluid mass of meconium there can often be seen a large number of small light yellow particles, usually no greater than a millimetre in diameter (Fig. 5). These 'meconium bodies' have been observed since Aristotle, but no one had put forward an adequate theory of their origin or possible role (Schmidt, 1897; Cramer, 1900).

Our interest in them stems from two observations: first, that occasionally these rather hard yellow bodies can be very large, producing obvious distortion of the intestine (Fig. 6 shows a caecum containing a cluster of very large meconium bodies), and secondly, the occasional finding of what seems to be a similar mass in a small segment of bowel, or in peritoneal tissue in the mass of distorted bowel adjacent to a congenital atresia. While we have seen no case of post-natal death due to these bodies, it remains possible that they are responsible for some cases of intestinal volvulus or obstruction *in utero* leading to intestinal atresia.

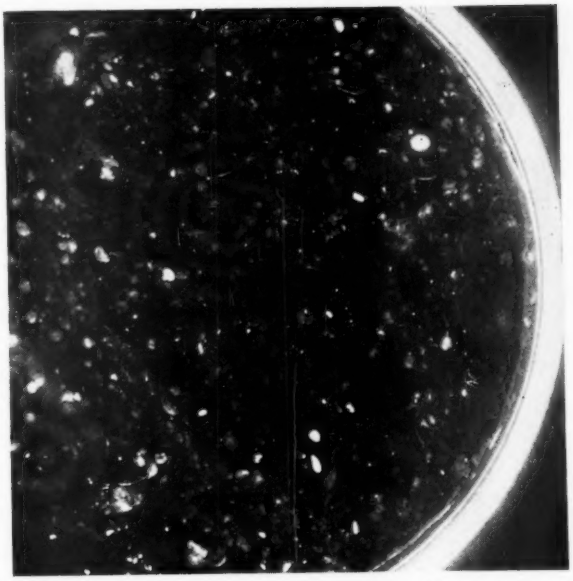

FIG. 5.—Photograph of some meconium lying within a petri dish, showing numerous meconium bodies. Scale approximately × 2.

FIG. 6.—Photograph of a caecum containing very large meconium bodies. The ileum and appendix are attached. Scale approximately × 1½.

FIG. 7.—Dissected specimen of caecum and descending colon from a child dying with general peritonitis, due to stercoral ulceration. The caecum shows ulceration of the mucosa, and adherent fragments of pale meconium. The narrow segment shows a site of perforation. Scale × ¾.

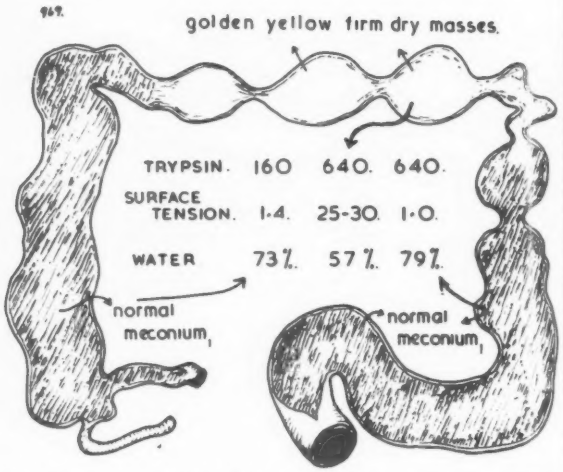

FIG. 8.—Diagram of the large bowel from a stillborn child, showing the position of the masses of inspissated meconium in the transverse colon and splenic flexure, and normal meconium elsewhere in the specimen. The tryptic activity, surface tension and water content from specimens from the indicated sites shown in the diagram.

Colonic Masses Causing Ulceration

Stercoral ulceration of the colon in the neonatal period is a well-recognized clinical entity. Four cases of spontaneous rupture of the sigmoid in newborn infants without associated intestinal abnormality were reported in 1884 by Zillner. While the majority of such cases are fatal, recoveries are possible by means of a colostomy even in the presence of pneumoperitoneum (Standard, 1952). The perforations may be single, but are frequently multiple, the case reported by Spörlein (1952) having four perforations. The theories of aetiology of these cases have been extremely varied (Standard, 1952): the over-enthusiastic use of enemas, immaturity of the bowel, congenital and acquired diverticula, primary vascular insufficiency, intestinal aplasia, birth trauma (Zillner, 1884) and even foetal enteritis due to the ingestion of infected amniotic fluid (Staemmler, 1953); others refer to intestinal 'dyscrasias' (Fèvre and Duhamel, 1952).

In the four cases of stercoral ulceration that I have examined at necropsy, the most striking features have been pale yellow concretions with overlying bowel wall necrosis and the complete absence of any significant histological abnormality in the bowel wall or pancreas, or any other organ examined. Fig. 7 shows two parts of the same colon from one of these cases; the wide specimen is of the caecum, with the ileum and appendix behind, and this contained a large, pale, friable mass of faeces causing degeneration of the mucosa but no ulceration. The narrow segment shows an ulcerated area in the region of the splenic flexure. These cases all show reactive changes and have been subjected to surgery.

It is from the chance finding of similar abnormal bowel contents in a stillborn infant during routine necropsy that an insight into the underlying basic lesion may be obtained. The large bowel of this stillborn child is represented in Fig. 8. The caecum and ascending colon and the lower descending colon, sigmoid and rectum contained apparently normal meconium, but the transverse colon and splenic flexure contained firm yellow masses. The tryptic activity, water content and surface tension of the colonic contents at different levels is shown also in Fig. 8, and this indicates that the meconium is normal in the first and last parts of the bowel, but that the concretions are grossly defective in water content. No gross differences in fat or protein content were detected.

If the case is significant, then it would appear that the neonatal ulceration seen clinically may be due to the abnormal absorption of water in the large bowel, a situation very similar to the localized plugs in the small intestine.

One of the major activities of the large bowel is the absorption of fluid and it seems likely that the faecal impaction may be due to an imbalance between the fluid absorption mechanism and that of propulsion of material along the colon.

Discussion

The localized abnormalities in meconium discussed above appear to be the effect of local functional abnormalities in the foetal intestine. Because infants that have survived do not appear to be in any way abnormal, it seems that the disorder is one

related to the peculiar state of apparent suspended animation of the foetal intestine late in pregnancy. There seems to be some alteration in the local water balance between the meconium and the affected segment of bowel that would to some extent explain the changes in physical properties of the meconium. The concentration of epithelial squames in meconium compared with the number present in liquor amnii gives some idea of the vast volume of amniotic fluid that must be swallowed by the foetus and this fluid absorbed through the intestinal wall. The foetal intestinal tract is no passive backwater (Becker, Windle, Barth and Schulz, 1940).

A further point on which we seem to be devoid of knowledge is the stimulation for the altered activity of the child's colonic and rectal activity after birth. Obstetric experience teaches us that a child in 'intrauterine stress' begins passing meconium, but it would be hardly likely that it is simply anoxia that stimulates the bowel.

There appears to be no relationship between intestinal plugs and meconium ileus, for the children do not seem to develop the later fibrocystic picture or to have an abnormal sweating mechanism. The other common disorder of the bowel in the newborn, 'megacolon', is unlikely to be a complete 'all-or-none' disorder, and it is possible that the ano-rectal plug group have some slight variation in normal maturity of the intestinal intramural plexus that our present knowledge does not enable us to recognize.

Perhaps, however, we know no more about the activity of the bowel in the foetus than Hippocrates did when he made the delightful statement 'The presence of excretion in the intestine of the newborn baby proves that the foetus sucks inside the womb'.

Summary

A group of clinical abnormalities of meconium are described.

It is suggested that the obstructing ano-rectal plug is related to an immaturity of the colonic rectal expulsive mechanism.

Intestinal meconium plugs and stercoral ulceration of the large bowel appear to be related to localized abnormalities in the water balance in the affected segment of bowel.

Much of the material used in this paper came from necropsies that we were able to carry out at the City General Hospital, Sheffield, through the courtesy of Dr. A. J. N. Warrack.

REFERENCES

Becker, R. F., Windle, W. F., Barth, E. E. and Schulz, M. D. (1940). *Surg. Gynec. Obstet.*, **70**, 603.
Berti, G. (1898). *Arch. Kinderheilk.*, **24**, 463.
Buchanan, D. J. and Rapoport, S. (1952). *Pediatrics*, **9**, 304.
Burger, P. (1938). *Gynéc. et Obstét.*, **37**, 176.
Cramer, H. (1900). *Dtsch. med. Wschr.*, **26**, 194.
Davy, J. (1844). *Med.-chir. Trans.*, **27**, 189.
Digonnet and Fèvre, M. (1943). *Mém. Acad. Chir.*, **69**, 297.
Emery, J. L. (1952). *Archives of Disease in Childhood*, **27**, 67.
—— (1954). *Ibid.*, **29**, 34.
Falls, F. H. and Jaffe, R. H. (1931). *Amer. J. Obstet. Gynec.* **22**, 409.
Farber, S. (1933). *J. Amer. med. Ass.*, **100**, 1753.
—— (1944). *J. Pediat.*, **24**, 387.
Feldman, W. M. (1920). *The Principles of Ante-natal and Post-natal Child Physiology*, pp. 191-3. London.
Fèvre, M. and Duhamel, B. (1952). *J. Chir.* (*Paris*), **68**, 5.
Fleury, J. (1952). *Arch. franç. Pédiat.*, **9**, 725.
Franklin, A. W. and Hosford, J. P. (1952). *Brit. med. J.*, **2**, 257.
Hymanson, A. and Kahn, M. (1919). *Amer. J. Dis. Child.*, **17**, 112.
Low, J. R., Cooper, G. and Cosby, L. (1949). *Surgery*, **26**, 223.
Mardner, W. (1909). *Prag. med. Wschr.*, **34**, 671.
Rapoport, S. and Buchanan, D. J. (1950). *Science*, **112**, 150.
Schmidt, F. C. T. (1897). *Vjschr. gerichtl. Med.*, Ser. 3, **13**, 320.
Shwachman, H., Pryles, C. V. and Gross, R. E. (1956). *A.M.A. J. Dis. Child.*, **91**, 223.
Spörlein, S. (1952). *Arch. Kinderheilk.*, **144**, 63.
Staemmler, M. (1953). *Virchows Arch. path. Anat.*, **323**, 143.
Standard, J. E. (1952). *Amer. J. Surg.*, **83**, 107.
Thelander, H. E. (1939). *Ibid.*, **58**, 371.
Ullmann, E. (1894). *Dtsch. med. Wschr.*, **20**, 37.
Weil, H. (1902). *Ibid.*, **28**, 776.
Zachary, R. B. (1957). *Archives of Disease in Childhood*, **32**, 22.
Zillner, E. (1884). *Virchows Arch. path. Anat.*, **96**, 307.

MECONIUM AND FAECAL PLUGS IN THE NEWBORN*

BY

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This paper deals with the clinical aspects of a series of cases, the pathology of which has been described in the preceding paper by Emery. The cases fall into two distinct groups but some relationship between these groups will be discussed later.

The first group consists of cases of rectal obstruction by meconium plugs. In the second group the obstruction was due to hard faeces and was complicated by stercoral ulceration.

Meconium Plugs

Paediatricians and many general practitioners have been made aware that surgery has much to offer in the treatment of intestinal obstruction of the newborn and many are on the look-out for the cardinal symptom of vomiting green material in the first 12 hours of life. Any child with this symptom should be suspected of having intestinal obstruction. If in addition the infant has not passed meconium in the first 24 hours or so, or has passed some abnormal meconium, there is a very strong presumption of obstruction and the child should be sent to a centre where the paediatric and surgical attention can be expected to be of a high standard.

It is not surprising that a number of cases presenting in this way have turned out to be something different from the usual types of neonatal obstruction, atresia, stenosis, volvulus, meconium ileus and Hirschsprung's disease. They have been obstructed by a terminal plug of meconium. Brief clinical details of four of these cases are as follows.

Case 1. An infant was admitted at the age of 40 hours with a history of vomiting bile-stained material since birth; no meconium had been passed. On examination the infant was fairly well, not dehydrated and had a somewhat full abdomen. Rectal examination produced a plug of thick meconium which was followed by a large quantity of normal meconium; the child had normal bowel action afterwards and was well.

Case 2. An infant was admitted at the age of 36 hours, vomiting since birth, and the vomitus had become brown. No meconium had been passed. The infant was well apart from some abdominal distension and rectal examination produced a similar plug of meconium after which bowel action was normal. Recently a sweat test was done on this child and the result was within the normal range.

Case 3. This infant was somewhat older when admitted, 6 days, but had been vomiting from the age of 4 hours and had only passed one meconium stool (and that a small one) at 36 hours. This child was not well, moderately dehydrated, with a full abdomen. Rectal examination produced nothing at all but a rectal wash-out yielded some plugs of meconium, after which bowel action was normal.

Case 4. A 32-hour-old infant was admitted who had repeatedly vomited brown material and had not passed meconium. The abdomen was full, the child moderately ill, and rectal examination did not reveal any faecal matter. Preparations were made for operation with a diagnosis of intestinal obstruction, but the child suddenly died. Necropsy showed that death was due to inhalation, resulting from intestinal obstruction by a meconium plug in the rectum.

More than 90 % of newborn infants pass meconium within the first 24 hours of life and probably another 7 or 8 % in the next 12 hours, and the only difference between the remaining 2 or 3 % and the cases described above is that the latter were vomiting bile-stained material and were therefore in danger of death by inhalation. The plug found in these cases was similar to that normally passed when the rectum is first emptied and to that found in the stillborn, but with a lower water content. It seems likely that the greater firmness of this plug is due to its remaining longer in the rectum rather than to any intrinsic abnormality of the meconium.

Faecal Plugs with Stercoral Ulceration

In the second group of cases the infants were admitted to hospital between 4 days and 5 weeks of age and were found to have a perforation of the colon overlying a hard mass of faeces. The following are brief summaries of six cases.

*A paper read at the meeting of the British Association of Paediatric Surgeons in London in July, 1956.

Case 5. This infant was admitted at the age of 4 days with a history of vomiting from the second day; meconium had been passed at 30 hours and also on the third day. The child was very ill, vomiting brown material with a distended abdomen. Radiographs showed free gas under the diaphragm. At operation a perforation of the sigmoid colon was found and the loop exteriorized. The child died shortly afterwards and at necropsy the sigmoid was deep red with some necrotic zones overlying faecal matter. The pancreas was normal and histology of the colon showed ganglion cells throughout.

Case 6. An infant of 5 days of age was admitted who had vomited about 15 minutes after every feed and had only passed two small meconium stools. After admission the child passed a few small loose brown stools for two days and then quite quickly became seriously ill, vomiting faecal contents and died suddenly. Necropsy revealed perforation of the ascending colon with a terminal respiratory infection. The histology of the pancreas and the colon were normal.

Case 7. This child came into hospital at the age of 9 days with increasing constipation and abdominal distension. Radiographs showed free gas in the abdomen. At operation no perforation was found and a transverse colostomy was made in the belief that Hirschsprung's disease was the cause. He died at the age of 15 days from peritonitis due to a perforation of the ascending colon and a similar perforation of the splenic flexure, distal to the colostomy. Histology showed ganglion cells in the colon and a normal pancreas.

Case 8. This child was sent into hospital by a paediatrician at the age of 7 days because she had vomited repeatedly some yellow fluid after feeds, and, although she passed four normal-looking meconium stools during the first 24 hours, there was no further spontaneous bowel movement. The infant was moderately ill, with a distended abdomen but shortly after rectal examination meconium was passed (quite obvious greenish black material), followed by a lot of gas and later softish faeces. She was sent home after four days but was admitted three days later moribund. She was vomiting yellowish-brown fluid and had not passed a stool since discharge. She was extremely dehydrated, with a distended abdomen, and rectal examination showed a small amount of hard faeces. She died within a few hours and necropsy revealed peritonitis due to perforation of the sigmoid colon overlying a mass of hard faeces. The pancreas was normal and ganglion cells were present in the distal colon.

Case 9. This infant had originally come into hospital at the age of 1 day because of abdominal distension and failure to pass meconium. Rectal examination produced some normal meconium and the child went home quite well. He was readmitted at the age of 4 weeks because he was underweight and the feeding régime was increased. Two days later he suddenly became extremely ill with vomiting and distension of the abdomen. At operation a perforation of the sigmoid colon was found and the loop was exteriorized. The child died and was found to have peritonitis and a gross congenital heart lesion. The pancreas was normal and the intramural plexus of the colon was quite normal.

Case 10. This was an infant of 5 weeks who had vomited fairly frequently since birth and had hard stools for some days before admission. The child had a renal tract infection which was treated with antibiotics and an enema produced some very hard faecal material. After two weeks in hospital the child became very ill, vomiting, with abdominal distension and not passing stools. The baby was thought to have Hirschsprung's disease, an impression which was enhanced at operation when a distended colon was found. A transverse colostomy was performed but the child died suddenly a few days later and was found to have a perforation of the sigmoid colon over some very hard faecal matter. Histology showed a normal pancreas and a careful study of the colon failed to confirm the impression of Hirschsprung's disease.

Discussion

Although this second group of cases is in some ways so different from the first, there are some findings in common in a few of the infants. One child in the first group (Case 3) passed meconium at 36 hours but nothing more until a rectal wash-out was given at 6 days. Clearly something more than a terminal ano-rectal plug was involved. Moreover, in the second group were several infants who passed little or no meconium in the first few days, and there must have been delay or difficulty in expelling meconium from the colon.

In the first group the possibility of a mild form of meconium ileus was considered but tryptic activity was present at a high dilution in the stools, and in the one case where a sweat test was done there was no evidence of an increased loss of salt.

Hirschsprung's disease was eliminated by the smooth course once the rectal plug was removed.

The most likely diagnosis in the second group of these cases seemed to be Hirschsprung's disease and on that account particular attention was paid to the intramural plexus at necropsy but no abnormality was found. The most striking features have been the hardness of the faecal contents and the fact that the perforation was usually overlying a hard faecal mass. In two cases deflation of the bowel proximal to this point had not prevented ulceration.

Perforation could have been due to a congenital defect in one segment of the bowel wall but no such defect was found. It seems more likely that there was a pressure necrosis of a normal bowel by a hard faecal mass and that the firmness of the faecal matter was due to excessive absorption of water. Excessive water take-up might be a peculiarity of the bowel wall but it is much more likely to be due to

delay in the passage of the contents of the colon on towards the rectum and then through the anus and it might be that some incoordination of large bowel action in these babies is a manifestation of immaturity of function.

Summary

Ten cases are described in which there was obstruction of the large bowel in the first few weeks of life.

Four of these cases come clearly under the heading of meconium plugs which can be relieved by rectal examination or rectal wash-out in a child who presents in the neonatal period as intestinal obstruction. In six cases there was incomplete obstruction of the colon by hard faecal matter between the ages of 4 days and 5 weeks and perforation of the bowel occurred in all cases.

Thanks are due to Dr. T. Colver, Dr. R. Gordon and Professor R. S. Illingworth for permission to include cases admitted under their care.

SEPTIC UMBILICAL ARTERITIS*

BY

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The number of cases of umbilical arteritis seen by surgeons in this country is small, but in view of the disastrous complications to which the condition may give rise, it deserves more consideration than is accorded to it in modern text-books of paediatrics and surgery. It therefore seems appropriate to review six cases of this condition seen in the last few years.

History

During the middle and later part of the last century thousands of infants in this country and on the continent died annually as a result of umbilical infection.

Two types were recognized: (*a*) Moist spreading gangrene of the umbilicus (hospital gangrene) when children died of toxaemia, septicaemia, peritonitis and occasionally rupture of the abdominal wall. (*b*) Erysipelas of the umbilicus, also called puerperal fever of the newborn, in which septicaemia was the common termination.

Both types were much commoner in institutions than in private practice and carried an appalling mortality. Both occurred in epidemic form, often but not always concurrently with epidemics of maternal puerperal infection. Outbreaks of umbilical sepsis were recorded by physicians all over Europe.

Trousseau (1844), in describing his cases, noted the occurrence of peritonitis and osteomyelitis, and pointed out that death could result from umbilical infection even when the umbilicus appeared to be normal.

Meynet (1857), in Paris, described an epidemic which affected 53 infants, 36 of whom died. Eighteen came to necropsy and of these 10 had peritonitis and in three there was septic umbilical arteritis. He treated umbilical sepsis with Canquoin's paste (zinc chloride in wheaten flour) apparently with some success. He stated that Ambroise Paré regarded the malady (umbilical sepsis) as so grave that he advised the surgeon 'not to raise a hand lest he be accused of having caused the death of the infant'.

Bergeron (1866) reported an epidemic at L'Hôpital Necker. Nine babies came to necropsy and all showed involvement of either vein or arteries or both.

Runge (1893), at La Charité Hospital, Berlin, found evidence of umbilical infection in 30 out of 36 babies dying of sepsis. He states that the infecting organism was either the streptococcus or the staphylococcus. He studied the method of separation of the cord in uninfected babies and recognized that obliteration of the umbilical vein and umbilical arteries is not brought about by exactly the same process.

At necropsy on 55 cases Runge found septic arteritis in all but one, whereas he found phlebitis only once. He gives a very full description of arteritis and periarteritis and states that in some cases the infection may reach right down to the internal iliac artery.

Lambert (1897) described a small epidemic in the Children's Hospital, New York.

Ritter von Reuss published his book *The Diseases of the New-Born* in 1914. In this interesting work there is a large section on the care and diseases of the umbilicus. By this date epidemic umbilical sepsis was rare in the hospitals in Vienna in which Reuss worked.

In 1916 Cullen produced his monumental volume on the umbilicus and its diseases, appropriately dedicated to his mother. He reviewed the literature on umbilical sepsis and describes in detail a large number of cases. He states that in some epidemics phlebitis and in others arteritis predominated.

The influence of Lister and Pasteur, improvements in the care of newborn babies and in general hygiene, had put an end to epidemics of florid umbilical sepsis by the time von Reuss and Cullen wrote, and from this time onwards references to umbilical arteritis almost disappear from the literature.

Cruickshank (1930) in his report on 'Causes of Neo-natal Death' found umbilical sepsis in seven cases in a series of 800 necropsies. He does not mention umbilical arteritis.

Henderson (1943) and Smith, Platou and Good

* A paper read at the meeting of the British Association of Paediatric Surgeons in London in July 1956.

(1956) are of the opinion that the incidence of omphalitis is low and is nearly always due to an enterococcus. They do not mention umbilical arteritis. These writers were reviewing sepsis in newborn babies.

In recent years most attention has been given to the condition by Morison, who in 1944 mentioned four instances of arteritis complicating 11 cases of umbilical phlebitis, and in 1952 illustrated the various routes of infection in his book *Foetal and Neo-natal Pathology*. Fig. 1 is reproduced from this publication.

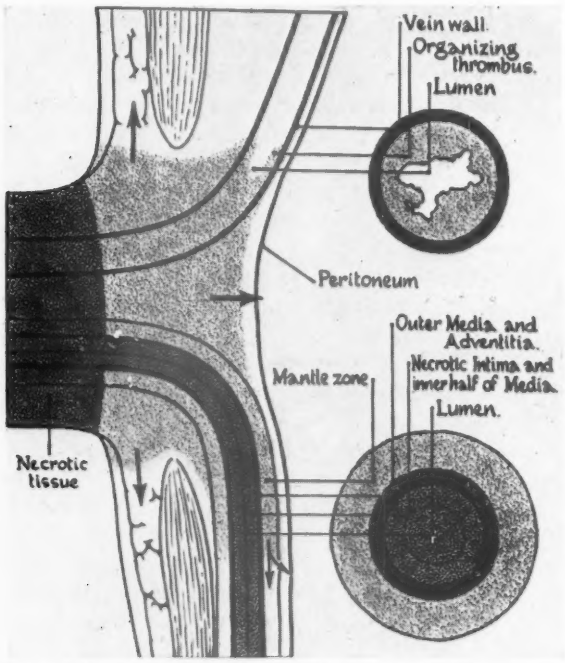

FIG. 1.—Diagram showing the routes along which infection from the umbilicus may spread (reproduced from Morison, 'Foetal and Neo-natal Pathology' by kind permission of Butterworth & Co. (Publishers) Ltd.). After birth the necrotic tissue of the umbilical stump separates. This provokes some inflammatory reaction but this is limited by fibroblastic reaction and only fibroblastic reaction should extend to the inner margin of the lightly stippled area. The inner half of the media and the intima of the umbilical arteries become necrotic, but this does not stimulate inflammatory reaction. Arrows indicate routes by which infection may spread beyond the granulation tissue barriers. Organisms invading the thrombus in the vein before this is organized may disseminate by emboli.

Pathogenesis

Soon after the child takes the first breath, the umbilical arteries contract strongly, blood flow ceases, and the arterial lumen becomes very narrow. The intima and the inner part of the media are thus deprived of blood supply and undergo aseptic necrosis.

The older writers postulated ante-natal, natal and post-natal infection. It is now considered that infection usually takes place within 48 hours of birth but that it may occur later in children with low resistance to infection, such as premature infants with large succulent cords. As separation of the cord proceeds, granulation tissue, which is resistant to the passage of microorganisms, normally develops, and epithelium quickly covers the granulation tissue.

Bacterial infection from the open umbilical wound may invade, lie latent in, or spread along, the lumen, the inner necrosing coats of the artery or the mantle zone of loose connective tissue around the artery, and suppuration in any one of these situations may spread to invade the others.

As infection delays or prevents obliteration of the vessels, umbilical bleeding is a common sequel. Indeed, bleeding from the umbilicus, if we exclude the haemorrhagic disorders, is probably always an expression of infection.

Depending upon the length of artery affected and its patency, the following sequence of events may result from infection of an umbilical artery:

(1) Sepsis in a segment of an umbilical artery, the iliac end of which is obliterated, carries the implications of any septic focus. If the umbilical end remains patent there will be chronic or intermittent purulent umbilical discharge. If the mantle zone is infected either primarily or secondarily, local or general peritonitis may result. Pus is prevented from pointing forwards by the tough fascia of the anterior abdominal wall. It may track along the course of the artery to point as an abscess in the scrotum or thigh. Infection may reach the blood stream to cause septicaemia through the small vessels of the anterior abdominal wall.

(2) If the infection involves the whole course of the vessel, the iliac end remaining patent, in addition to the possibilities already mentioned, bacteria from the lumen of the umbilical artery may be released into the blood stream and a rapidly fatal septicaemia result. Should a periarterial abscess spread the whole length of the vessel, pus would ultimately collect around the iliac vessels, where it might in time cause erosion and weakening of the wall of an iliac artery. I have not found a description of this latter happening in the literature, though it seems the most likely explanation of one of the cases detailed below.

Case Reports

Case 1. Stephen O. was born at home and admitted at the age of 7 weeks. No information is available about the condition of the umbilicus in the post-natal period. He had made good progress, apart from a probable urinary infection at 5 weeks, when the umbilicus started to discharge pus. Thirty-six hours

before admission he had become extremely fretful, refused his feeds and vomited.

He was found to be very ill with grunting respirations, pallor, dehydration and the appearance of shock.

The abdomen was distended and tympanitic. There was guarding and a possible mass on the left below the umbilicus.

Clinical and radiological findings suggested peritonitis.

At laparotomy the abdomen was full of seropurulent fluid, no cause for which was found. The child died 48 hours after the onset of the illness.

At necropsy, the umbilicus was discharging but not inflamed. A segment, 1 cm. in length at the iliac extremity of the left umbilical artery, was obliterated and appeared normal. The whole of the left umbilical artery, apart from this small lower segment, was swollen and contained blackish clot, and there was a large loculated periarterial abscess with rather fibrotic walls, containing yellow pus.

FIG. 2.—Section of umbilical arteries in Case 2 showing dense inflammatory infiltration in mantle zone reaching peritoneum, arterial walls free of inflammatory reaction, and masses of bacteria along margins of patent arterial lumina.

Staphylococcus pyogenes was grown from the peritoneal fluid, the abscess and the lumen of the artery.

In this child the mantle zone was infected within the immediate post-natal period. Infection spread inwards to involve the lumen of the artery. By 5 weeks of age a large periarterial abscess had formed from which the peritoneal cavity became infected, and from which pus discharged at the umbilicus.

Case 2. Stephen McC. was born in hospital, a normal healthy baby until the seventh day, when there was bleeding from the umbilicus. On the ninth day the child refused feeds and vomited repeatedly; the vomitus contained blood.

He was admitted on the eleventh day having been ill for 36 hours. He was pale and collapsed with a subnormal temperature and tachycardia. The limbs were cold and mottled, skin petechiae were noted, examination of the chest showed widespread fine crepitations and the abdomen was distended. The blood chemistry was fairly normal apart from a blood urea level of 216 mg. %. The white cell count was 10,000 per c.mm. with a normal differential count.

The child died in convulsions 44 hours after the onset of the illness.

At necropsy there was no discharge from the umbilicus, but the depths of the cavity were purulent and haemorrhagic.

The umbilical arteries were patent throughout, the part adjacent to the umbilicus being filled with black clot.

Microscopically (Figs. 2 and 3) the inner part of the wall of the arteries showed only the normal involutional necrosis but masses of cocci were seen here and in the lumen. There was widespread periarteritis and early fibrinous peritonitis.

The lungs were solid with haemorrhagic pneumonia. Microscopically, embolic lesions were seen in the pancreas and both kidneys.

Staphylococcus pyogenes was grown from the umbilicus and the bronchi.

The mantle zone was infected at birth and this led to a periarterial abscess, from which, as in Case 1, the peritoneum became infected. The infection in the lumen and inner part of the wall of the artery had probably been present since birth (it caused no reaction) as the organisms proliferated in avascular necrotic tissue. The lumen of the umbilical artery was patent throughout, and from it cocci were discharged into the internal iliac artery. A virulent septicaemia resulted with embolic lesions in the lungs, pancreas, kidneys and skin.

Case 3. John McC., aged 4½ years, was born in hospital.

When seen as an out-patient the umbilicus had been discharging pus for three months. *Staphylococcus pyogenes* was grown from the umbilical discharge. A probe passed from the umbilicus downwards and to the left.

At operation the left umbilical artery from the umbilicus to the level of Poupart's ligament was as thick as a cigarette. The iliac extremity was a fine, string-like structure. The peritoneum was adherent to the infected artery and posteriorly omentum was adherent to the peritoneum. The infected tissue was removed *en bloc*. Sections showed granulation tissue heavily infiltrated with plasma cells, a few polymorphs and eosinophils. Arterial structure could not be defined.

We concluded that infection at birth, either luminal, intra-mural or periarterial, had remained quiescent until the child was $4\frac{1}{2}$ years old.

FIG. 3.—Higher power view of same section as Fig. 2 above.

Case 4. Carol S. was born at home. The cord was a little late in separating, but the umbilicus dried up normally. On the 12th day there was a transient discharge of yellowish brown material from the umbilicus. On the 21st day she was admitted to Noble's Hospital, Isle of Man, because of severe bleeding from the umbilicus. Blood continued to seep for a week and was followed by a purulent discharge. The temperature rose to 101-103° F., and the haemoglobin fell to 52 %. The upper abdomen was distended and superficial veins were dilated, the liver being enlarged. A blood transfusion was given and she was transferred to our care at the age of 8 weeks.

The above findings were confirmed and a tender mass was felt in the right iliac fossa which could just be touched from the rectum. A plain film showed nothing abnormal but a radiograph after iodized oil had been injected through the umbilicus showed pooling of the opaque medium below and to the right of the umbilicus (Fig. 4).

The discharge from the umbilicus grew *Staphylococcus pyogenes* and diphtheroids.

At operation the peritoneal cavity was almost obliterated by adhesions. The mass was extra-peritoneal and was seen to pulsate. During the enlargement of the incision to obtain better exposure, torrential arterial bleeding started which was controlled with some difficulty by applying digital pressure to the aorta.

The swelling, which was about the size of a tangerine, was incised and found to contain a cavity into which a large artery (either the internal or common iliac) opened. The opening was oversewn, a portion of the wall of the cavity was removed and the cavity obliterated by several layers of silk sutures. A mass of inflammatory tissue was seen in the line of the umbilical artery, and was left undisturbed. The child lost 2 pints of blood at operation, which was replaced, the haemoglobin being 76 % before and 66 % after operation.

Post-operatively the abdominal distension and superficial veins disappeared, the haemoglobin level rose to a normal figure, but the umbilicus continued to discharge and a second operation was required to drain the umbilical end of the artery.

Section of the tissue removed at the first operation showed it to consist of laminated fibrin in the interstices of which were erythrocytes and numerous polymorphs. In the inner layers there was some early calcification.

It appeared that the right umbilical artery had been infected at birth. Severe bleeding at 21 days suggested that the whole length of the artery was patent. It is not possible to say if the infection which caused it to remain patent was primarily in the lumen, or secondary to a periarteritis which also caused peritonitis, probably at the time of the febrile illness in Noble's Hospital. The periarteritis spread

FIG. 4.—Injection through umbilicus in Case 4 showing large collection of iodized oil in right iliac fossa.

FIG. 5.—Radiograph of Case 5 after injection of iodized oil. Right periarterial abscess.

to the internal iliac artery where an abscess formed, weakening the arterial wall and ultimately causing the formation of an aneurysm. There was no evidence of bacterial embolism, and it is unlikely that the aneurysm was of embolic origin. This case is probably unique.

Case 5. Catherine M.D. was seen as an out-patient at the age of 4 weeks. She had been delivered by a midwife at home. The umbilicus had discharged since separation of the cord.

A probe could be passed downwards and to the left from the umbilicus. There was profuse purulent discharge from which *Staphylococcus pyogenes* was cultured.

Radiographs after the injection of iodized oil (Fig. 5) showed the typical picture of pooling round the left umbilical artery.

Following the injection the discharge gradually diminished and six weeks later the umbilicus was dry; the white cell count and the erythrocyte sedimentation rate were normal.

This case is probably one of periarteritis involving a short segment of the artery, drainage being improved by the injection. It is probable, but not certain, that this baby will have no further trouble.

Case 6. David S. was born in hospital by internal

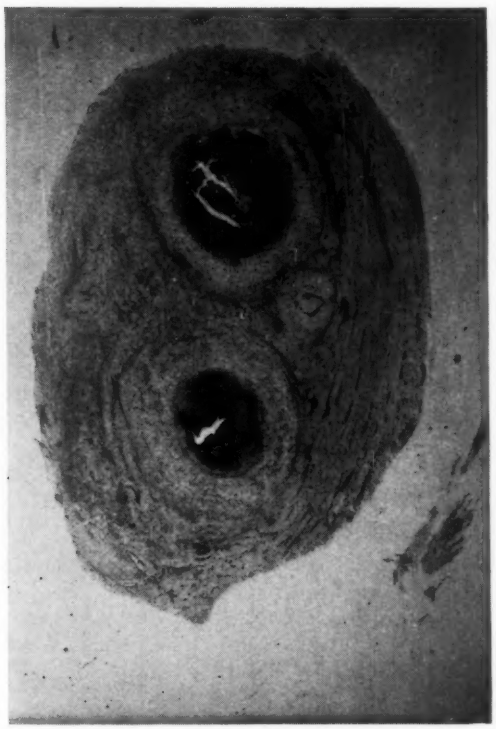

FIG. 6.—Section of umbilical arteries in Case 6 showing minimal infiltration in mantle zone, with inflammatory destruction of inner portion of arterial walls.

version and forceps delivery after 37 weeks' gestation. Five pounds in weight, he was considered a normal infant.

At 2 days of age he refused to feed, looked ill, showed deepening jaundice and para-umbilical redness, and died the same day.

At necropsy, the cord was still attached. The umbilicus was moist and yellow. The umbilical vein appeared normal.

The arteries contained purulent material and were patent throughout. Microscopy showed that the mantle zone was uninfected (Figs. 6 and 7). Infection was limited to the inner zone of the arterial wall and the lumen, which were heavily infiltrated with pus cells. In one artery the infection was most severe in the intramural zone, but was leaking through into the lumen. In the other artery the inner wall consisted only of pus cells.

There was a tentorial tear, without subdural bleeding, but extensive central cerebral softening.

A paracolon bacillus was isolated from the umbilicus, the umbilical arteries, the brain and the blood stream.

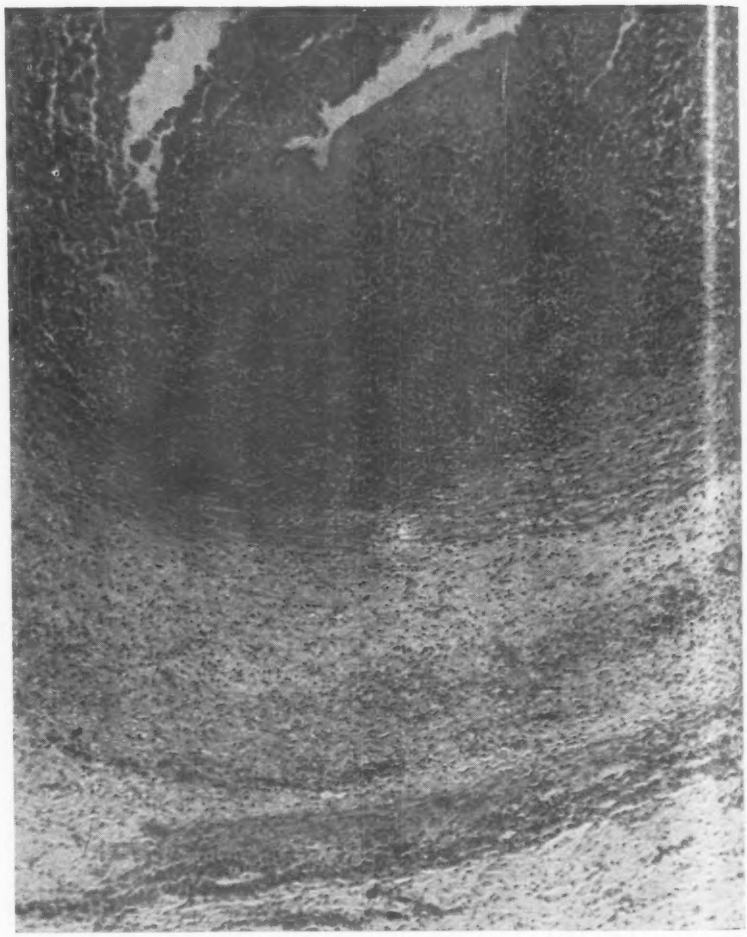

FIG. 7.—Higher power view of same section as Fig. 6.

Conclusions

The florid umbilical sepsis of the last century is now extremely rare in the western world, but infection of the open umbilical wound still occurs. One of its manifestations is septic umbilical arteritis. This condition may, if unrecognized, lead to various serious complications and cause death from septicaemia. Umbilical arteritis should be considered a possible source of infection when a child's abdomen is opened for peritonitis and no obvious cause is found. It seems possible that as the incidence of resistant strains of bacteria increases, umbilical arteritis and its complications will be seen more often in the future. In this small series *Staphylococcus pyogenes* was probably the infecting organism in five out of the six cases.

I should like to thank Dr. Edward Hall, Pathologist to Alder Hey Children's Hospital, for his help, Mr. P. P. Rickham for allowing me to include his cases and Dr. Barbara Ockenden for necropsy reports.

My thanks are also due to Dr. J. E. Morison for permission to reproduce Fig. 1 from his book.

REFERENCES

Bergeron, H. (1866). *Remarques sur une épidémie de gangrène de l'ombilic.* Thèse de Paris, No. 59.
Cruickshank, J. N. (1930). *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 145.
Cullen, T. S. (1916). *Embryology, Anatomy, and Diseases of the Umbilicus.* Saunders, Philadelphia.
Henderson, J. L. (1943). *Edinb. med. J.*, **50**, 535.
Lambert, S. W. (1897). *Med. News* (*N.Y.*), **70**, 557.
Meynet, C. H. P. (1857). *Épidémie d'érysipèle et d'ulcération de l'ombilic chez les nouveau-nés.* Thèse de Paris, No. 156.
Morison, J. E. (1944). *J. Path. Bact.*, **56**, 531.
—— (1952). *Foetal and Neonatal Pathology*, p. 314. London.
Reuss, A. R. von (1914). *Die Krankheiten des Neugeborenen.* Berlin. Eng. trans. (1920). *The Diseases of the Newborn.* London.
Runge, H. M. (1893). *Die Krankheiten der ersten Lebenstage*, 2nd ed., p. 56. Stuttgart.
Smith, R. T., Platou, E. S. and Good, R. A. (1956). *Pediatrics*, **17**, 549.
Trousseau, A. (1844). *J. Méd.* (*Paris*), **2**, 1.

INTRALUMINAL INTESTINAL CALCIFICATION IN THE NEWBORN*

BY

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Meconium ileus is now a well recognized entity and I do not need to dwell upon it in this paper. It is not only the condition in which an abnormality of the intestinal contents causes obstruction in the neonatal period. In recent years more attention has been paid to meconium plugs as a cause of blockage (Clatworthy, Howard and Lloyd, 1956). The object of this paper is to draw attention to a third condition causing intraluminal obstruction in early infancy. I apologize for reporting a single case. The condition seems to be extremely rare; at any rate I have found very few pertinent references in the course of a careful search through the literature. I wonder, however, whether an increased interest in this syndrome may not result in further cases being reported, as has happened before with many other diseases which were originally thought to be rarities. I apologize also for not being able to throw any light upon the causation of this lesion. In spite of a large volume of clinical and biochemical investigation carried out upon this particular infant, the disease remains surrounded by mystery. Any light shed on the little understood physiology of the neonatal intestinal tract is of value and this is a further reason for the publication of this case.

Case History

Gillian was admitted to the Alder Hey Neonatal Surgical Unit on August 25, 1955, when 37 hours old, a one-month premature infant weighing 5 lb. She was the first child of parents both of whom had been treated for infertility for several years. The infant had vomited repeatedly since birth and the vomitus had become bile-stained; she had not passed any meconium.

On admission her general condition was fair. There was some abdominal distension and a radiograph in the upright position showed numerous fluid levels. On the right side of the abdomen a number of calcified, worm-like-shadows could be seen (Fig. 1). In view of the clinical and radiological findings a provisional diagnosis of low small bowel obstruction associated with meconium peritonitis was made and she was operated upon two hours after admission. At laparotomy the jejunum and upper two-thirds of ileum were found to be bluish and distended with fluid. The lower ileum and colon were collapsed and contained a little semi-solid material. There was a Meckel's diverticulum, but apart from this no anatomical abnormality could be discovered. The obstruction was now thought to be due to meconium ileus; we were, however, mystified about the calcification in the radiological picture, as there was no evidence of meconium peritonitis. An enterostomy was performed on the most distal loop of distended ileum, through which a rubber catheter was passed proximally. A large amount of greenish fluid material containing many firm

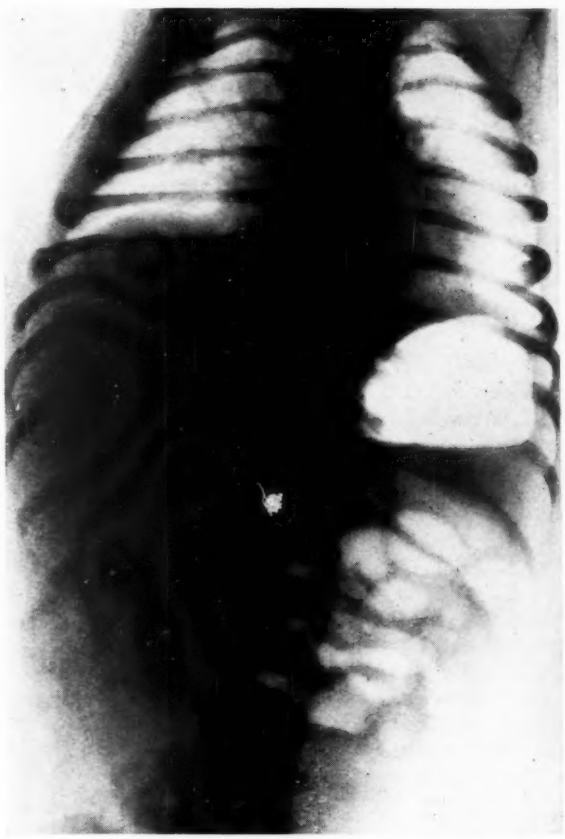

FIG. 1.—Radiograph of the abdomen showing calcified shadows on the right side.

* A paper read at the meeting of the British Association of Paediatric Surgeons in London in July, 1956.

yellow granules was aspirated. The catheter was then withdrawn and passed with some difficulty down the ileum. Saline was injected with some force and by repeated injections and massaging the gut, it was ultimately possible to evacuate the ileum and to pass the catheter into the caecum and empty the whole colon and rectum. The gut distal to the enterostomy was filled with soft, snowy white material containing similar yellow granules to those found in the proximal intestine. The material did not appear to adhere unduly to the wall of the intestine and was evacuated in the shape of long, worm-like stools. When the proximal and distal intestine was completely cleared, the enterostomy was sutured and the abdomen closed.

Post-operatively the child's condition was quite good; she was placed on intravenous infusions and continuous gastric suction. During the subsequent days large amounts of bile-stained fluid were aspirated and the bowels did not open, although bowel sounds could be heard. By August 31 her condition had deteriorated and on September 1 (a week after the original operation) it was decided to re-open the abdomen.

At the second operation the proximal intestine was found to be distended with thickish fluid identical with that found at the first operation; there was no mechanical obstruction. At about the level of the Meckel's diverticulum the intestinal content became semi-solid and was only with difficulty squeezed along the intestine. A double-barrelled ileostomy was performed at the site of the Meckel's diverticulum and the intestine was completely emptied right up to the duodenum by aspirating its contents through a rubber catheter; the distal ileum and colon were similarly cleared.

Post-operatively the child's condition was poor, the temperature subnormal, but over the next few days she gradually improved and by September 3, many bowel sounds could be heard on auscultation. Feeding with glucose water, and, rather irrationally, pancreatin, was started although the stomach aspirations were still bile-stained and contained trypsin. The baby started to vomit large quantities of bile-stained material and feeds were discontinued on September 4. The ileostomy was washed out with no result. On September 5 a little 'lipiodol' was given by mouth and the child screened. The oil passed rapidly through the small intestine. On the next day (September 6) the child was found to have lost a lot of weight and it was decided that the calory intake must be increased and she was therefore tried on breast milk feeds. Vomiting became again so profuse that the feeds had to be discontinued. Discouraged by this we did not resume oral feeding, but on September 10 a catheter was passed upwards through the ileostomy opening and a continuous drip of protein hydrolysate given. Another catheter was passed downwards through the ileostomy opening and a continuous 10 % glucose drip was administered. The resulting calory intake, small as it was, improved the general condition of the child. Oral feeding was again attempted with glucose water on September 15 and with peptonized milk two days later, but soon had to be discontinued and the child put back on continuous gastric suction because of profuse bile-stained vomiting. On September 18 we attempted oral feeds with protein hydrolysate, again causing profuse vomiting. On the following day (September 19) we again attempted milk feeds with the same result and thereafter, apart from small feeds of glucose water, no further attempt at oral feeding was made.

The child had by now been on continuous intravenous infusions for three weeks and although her hydration and electrolyte balance had remained relatively constant, we were unable to give her enough calories and wasting was marked. During the fourth week her general condition gradually deteriorated. She developed pneumonia, attacks of cyanosis and Cheyne-Stokes breathing and finally collapsed and died 28 days after the original operation. During this time she had received five blood transfusions and 25 separate infusions of diluted plasma as well as large amounts of crystalloid intravenous solutions. In spite of continuous syphonage of her intestinal contents by gastric suction her blood chemistry was kept more or less within reasonable limits.

Laboratory Investigations. Many biochemical investigations were performed during the four weeks of life. The serial investigations of the blood urea, serum chloride alkali reserve, serum proteins and serum potassium showed no abnormality. Intracellular electrolyte analysis of the red blood cells showed no striking abnormality. The serum calcium, calcium ions, phosphate and alkaline phosphatase of both the infant's and the mother's blood were repeatedly estimated and found to be within normal limits.

The stools evacuated at the first and second operation received special attention. Radiography of the whitish material expressed from the colon showed numerous flakes of calcium corresponding to the opacities which were seen in the pre-operative radiograph of the abdomen (Fig. 2). In these first stools there was no trypsin, but repeated subsequent analysis both of duodenal juices and ileal contents were always strongly positive for trypsin.

Analysis of the meconium obtained at the first operation was carried out and compared with meconium obtained from normal infants of the same age. As will be seen from Table 1, the only significant difference (as was to be expected) was in the calcium content (five times

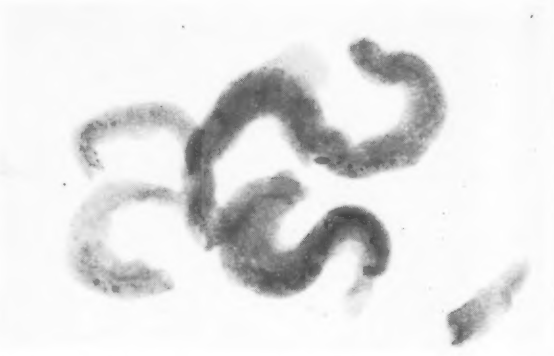

FIG. 2.—Radiograph of meconium expressed at first operation. There are numerous opacities due to calcification.

normal) and phosphorus content (eight times normal); the iron content of the meconium was definitely increased, but still so small that it was found impossible to estimate it quantitatively.

TABLE I
ANALYSIS OF NORMAL AND ABNORMAL MECONIUM

Meconium	Gillian	Normal
Dry weight	10·5% of wet weight	22%
Total ash	7.2% of dry weight	4·3%
Na.	0·61%	0·65%
K.	0·12%	0·29%
Ca.	0·62%	0·12%
P as P	0·52%	0·06%
N2.	5·7%	4·7%

Necropsy. A careful necropsy and subsequent histological examination performed by Dr. C. Jones did not throw much light on the aetiology of the condition. There was no mechanical intestinal obstruction, the lower small intestine was dilated, the upper of normal calibre. It was noticed that the intestinal contents were more solid than usual, the upper jejunum containing solid instead of fluid material. The only other abnormal finding was a hydronephrotic left kidney.

Histologically the only positive findings were moderate fatty changes in the liver. The pancreas and lungs were normal. There was no evidence of mucoviscidosis. The intestine was histologically normal; no abnormality of innervation of the gut could be observed, the ganglion cells appeared normal in size and distribution.

FIG. 3.—Meconium peritonitis with complete left inguinal hernia. Radiograph three days after operation shows calcification of meconium in the scrotum.

Discussion

Intra-abdominal calcification in the neonatal period is commonly found in meconium peritonitis, calcification occurring in the bowel wall or in meconium extruded into the peritoneal cavity (Neuhauser, 1944). The calcification in the bowel wall is probably the result of intra-uterine perforation of the intestine (Forshall, Hall and Rickham, 1952). That meconium in the peritoneal cavity can calcify within a matter of a few days was observed by Rudnew in 1915. We have recently seen a case with free meconium but no calcification in the peritoneal cavity. At operation we failed to suck the meconium out of the sac of a large complete inguinal hernia. There was radiological evidence of calcification within the scrotum three days after operation (Fig. 3). Calcification of meconium within the bowel lumen has never been demonstrated in meconium peritonitis.

Meconium plugs occasionally show microscopic evidence of calcification, as was first shown by Trump in 1912, but, as in faecoliths, the calcification is localized and removal of the plug is all that is necessary to prevent further calcification and cure the patient.

Intraluminal calcification has only been described twice in the literature, in both cases it was associated with mechanical intestinal obstruction. In a baby girl described by Camp and Roberts (1949) there was an extreme ileal stenosis for which an ileo-transverse colostomy was performed. The intestinal content was microscopically and radiologically very similar to that observed in our case. Unfortunately the child died soon after operation and we do not know whether the subsequent clinical course would have been the same as in our case. At necropsy no abnormality was discovered. The meconium was unfortunately not analysed. No blood chemistry studies were carried out.

A very similar case associated with anal atresia was reported by Khilnani, Wolf and Arnheim (1955). Once the obstruction had been removed this patient had no further trouble, passing normal stools, and made a perfect recovery. The meconium was very similar to that observed in our case; the blood chemistry of patient and mother was normal.

Our case appears therefore to have several unique features; she had no organic obstruction and following complete removal of the calcified meconium the intestinal content re-calcified and re-solidified. These features make one think of mucoviscidosis or long segment Hirschsprung's disease, but there was

no evidence of either. We are thus left with the supposition that this case constituted a separate clinical and pathological entity and that the lesion was due to the nature of the meconium, possibly due to some deficiency of gastro-intestinal function. It is unlikely that the enormous increase in the calcium content of the meconium can be derived from swallowed amniotic fluid, which contains very little calcium indeed (Camp and Roberts, 1949). It is more likely that the excess of calcium in our case was excreted into the intestine.

Unfortunately all our biochemical and histological investigations having been inconclusive, we have no explanation to offer, nor can we put forward any helpful therapeutic suggestions. During recent years we have learned a great deal about conditions which I should like to call 'meconium diseases', such as cystic fibrosis of the pancreas, mucoviscidosis, meconium peritonitis and meconium plugs, but the existence of the clinical entity described in this paper shows that we have still a long way to go before we understand the mysterious processes governing the formation of meconium and intestinal secretions in the foetus.

Summary

A case of intraluminal calcification of meconium, the third to be described in the literature, is reported. The nature of the causative lesion is unknown and in spite of extensive biochemical and histological studies no further light can be thrown upon the aetiology of the condition.

I should like to thank Miss Isabella Forshall for her help in preparing this paper.

References

Camp, R., and Roberts, M. H. (1949). *Amer. J. Dis. Child.*, 78, 393.
Clatworthy, H. W., Howard, W. H. R., and Lloyd, J. (1956). *Surgery*, 39, 131.
Forshall, I., Hall, E. G., and Rickham, P. P. (1952). *Brit. J. Surg.*, 40, 31.
Khilnani, M. T., Wolf, B. S., and Arnheim, E. E. (1955). *J. Mt Sinai Hosp.*, 22, 58.
Neuhauser, E. B. D. (1944). *Amer. J. Roentgenol.*, 51, 421.
Trump (1912). *Jb. Kinderheilk.*, 76, 678.

TISSUE CULTURE AS A POSSIBLE AID IN RECOGNIZING THE ORIGIN OF CYSTIC HYGROMA*

BY

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For many years the neck and the axilla in the child have been recognized as the commonest sites for cystic hygroma. Goetsch (1938) gave an extensive clinical and pathological survey of this condition and reported 12 fresh cases of varying ages. Recently two cases have been seen in the Royal Infirmary, Dundee, which behaved clinically in quite different ways.

Tissue culture was used by Sano and Bello (1949) as a means of differentiating morphologically identical cells in lymph nodes. In the light of this and of the reputed lymphatic origin of cystic hygroma we have successfully grown material from an axillary hygroma. This appears to be the first occasion on which this has been achieved.

Material

Both babies were girls. The first (Fig. 1) was seen within 48 hours of birth when the very large swelling was not interfering with either respiration or feeding. The tumour could be transilluminated readily and the clinical appearance was that of a cervical cystic hygroma. No immediate treatment was advised. Over the months the tumour rapidly regressed and at 8 months showed only surplus skin and a tiny nodule 0·5 cm. in diameter left in the neck.

The second infant had a cystic swelling in the left axilla which extended forward from the mid-axillary line to the region of the left nipple. It had been present since birth and slowly but steadily increased in size until at 6 months of age the tumour measured approximately 8 cm. by 5 cm. with a small firm nodule 1 cm. in diameter near the centre. Again it could be transilluminated and the clinical appearance was that of an axillary cystic hygroma. On March 5, 1956, wide excision was done and the cysts emptied and the raw surfaces swabbed with carbolic. Histological sections reported on by Dr. Wallace Park showed the features of a cystic hygroma with endothelial lined spaces in a fibro-fatty framework and no significant quantity of lymphatic tissues in the area examined (Fig. 2). A representative piece of tissue was selected for tissue culture and rapidly transferred to the laboratory.

FIG. 1.—Large cervical cystic hygroma which regressed over a period of three months.

Tissue Culture Technique and Results

Ten pieces of tissue were put up in standard hanging drops using equal parts of plasma and embryonic extract. They were incubated for 48 hours at 37°C and showed no evidence of growth.

A further six pieces of tissue were placed in roller tubes according to the method of Cameron (1950), and 0·7 ml. of supernatant fluid, consisting of 50 % tyrode solution, 30 % horse serum and 20 % embryonic extract, was added to each tube and they were rotated at 12 revolutions per

* A paper presented at the meeting of the British Association of Paediatric Surgeons in London in July, 1956. This is a preliminary communication.

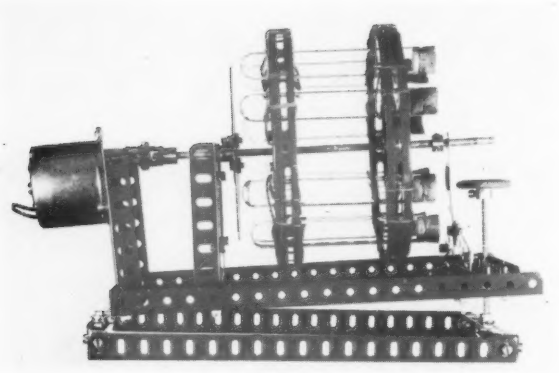

FIG. 3.

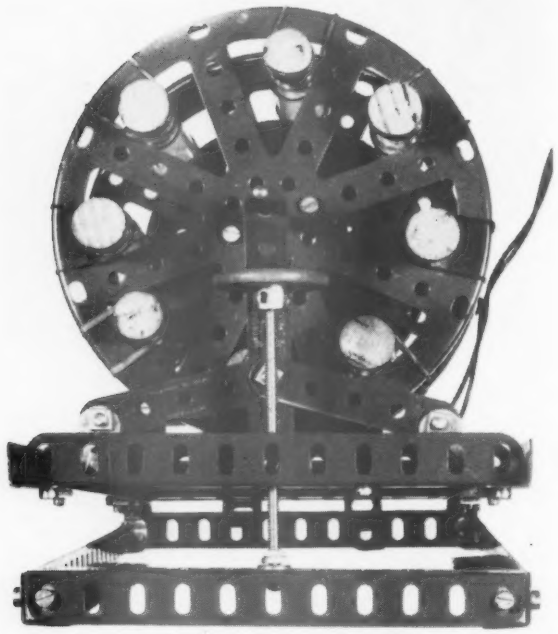

FIG. 4.

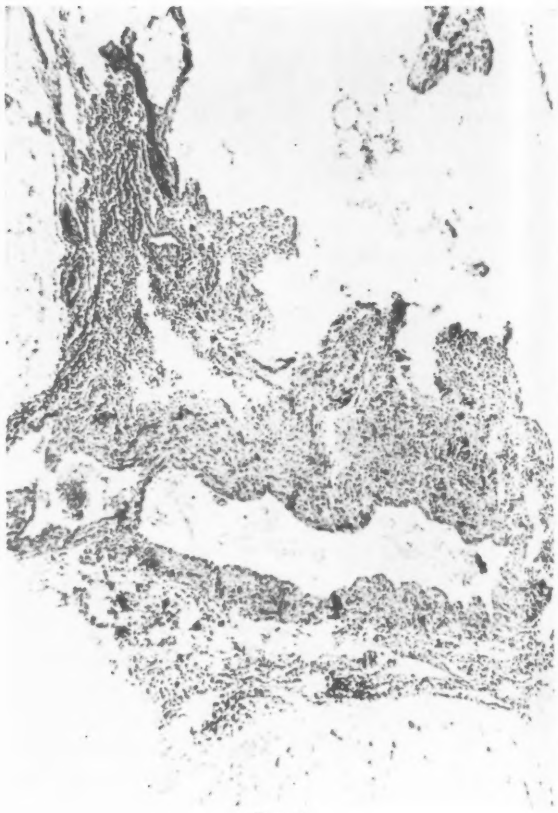

FIG. 2.

FIG. 5.

FIG. 2.—Histological section (low power) from axillary cystic hygroma —also used for tissue culture.

FIG. 3.—General view of apparatus for rolling tubes.

FIG. 4.—End-on view showing disposition of tubes in same apparatus as Fig. 3.

FIG. 5.—Low magnification view of growing explant.

hour in the drum arrangement shown in Figs. 3 and 4. This small roller tube drum followed the design of Szabó (1956) but was constructed from 'meccano'. Culture was continued for four days and three of the explants showed growth (Fig. 5). Finally the explants with growth were fixed and stained *in situ*. Microscopic examination of the proliferating cells showed pleomorphism.

Discussion

These two infants demonstrated opposite behaviour in two apparently similar lesions. It has usually been assumed that a cystic hygroma represented a maldevelopment of lymphatics at the site of occurrence. In the first infant the spontaneous regression could be explained on the basis of a multilocular cyst with communications between the loculi and one or two ultimate drainage channels. Such a state of affairs is occasionally seen in multilocular solitary cysts of the kidney. Wynn-Williams and Morgan (1950) reported a lymphangiomatous solitary cyst of kidney but study of their report and of material from a similar case (Attwood and Grieve, 1956) does not confirm the lymphangiomatous nature of these renal cysts.

The differing behaviour in the second child could be explained by the macroscopic and microscopic demonstration of a very large number of cysts varying in size from 1 mm. or less to around 1 cm. in diameter. Nothing about the structure suggested communication between the cysts.

Sano and Bello's work indicated that tissue culture might throw light on the origin of the lining cells. Using a simple roller-tube technique vigorous growth was obtained in three of the explants made. The cells were pleomorphic but their exact nature has not yet been determined.

Summary

The differing behaviour of an axillary and a cervical cystic hygroma has been described. With a simple roller tube tissue culture technique explants from the axillary tumour have been grown successfully. Pleomorphism was present in the outgrowths. Some of the cells were fibroblasts but the others have not yet been identified.

The cervical hygroma disappeared spontaneously and the possible similarity in structure to certain renal cysts has been emphasized. There was, however, no evidence to suggest that such renal cysts were lymphangiomatous in nature.

Mrs. Agnes Halley, Department of Anatomy, gave invaluable technical assistance and Miss Allison Thomson and Mr. Murray Ettle, Department of Surgery, were responsible for the manuscript and photography respectively.

References

Attwood, H. D. and Grieve, J. Unpublished data.
Cameron, Gladys (1950). *Tissue Culture Technique*, 2nd ed. New York.
Goetsch, E. (1938). *Arch. Surg. (Chicago)*, **36**, 394.
Sano, M. E. and Bello, C. T. (1949). *Amer. J. Med.*, **6**, 509.
Szabó, G. (1956). Personal communication.
Wynn-Williams, D. and Morgan, A. D. (1950). *Brit. J. Surg.*, **37**, 346.

TENSION EMPHYSEMA IN INFANTS*

BY

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The condition of obstructive emphysema confined to one lobe of a lung has aroused considerable interest because of the lack of uniformity in the pathological conditions found in specimens removed either at operation or necropsy.

Lobar emphysema is usually confined to one of the upper lobes or the right middle lobe. The affected lobe is grossly over-distended, causing mediastinal displacement and if this condition occurs in the neonatal period and is not relieved by lobectomy it may be rapidly fatal. In other cases a history of wheezing and of some difficulty in breathing over a period of months may be obtained. Any respiratory infection will cause an increase in the symptoms and the diagnosis is usually made by *x*-ray examination during a hospital admission necessitated by one of these attacks.

The commonest abnormality found in our cases was a deficiency of cartilage in the bronchial wall allowing the bronchus to collapse and producing an obstruction to the expulsion of air from the affected lobe during expiration. It is the purpose of this report to present a series of nine cases of lobar emphysema, in seven of which the same pathological condition was found in the affected lobe and to suggest that this may be the essential abnormality in the production of the condition.

Case Reports

Case 1. N.C., a boy, was born on June 8, 1953. It was noted soon after the birth of this infant that the apex beat was on the right side. Radiological examination confirmed the diagnosis of mediastinal displacement, and a diagnosis of tension cyst on the left side was made. A needle introduced into the left side of the chest and connected to an underwater drain failed to give relief and the baby died in a few hours. Necropsy revealed emphysema of the left upper lobe, the bronchus to the lobe being unduly soft and compressible. Sections of the bronchus showed that its walls were entirely devoid of cartilage. The left main bronchus and the bronchus to the lower lobe were normal.

Case 2. The demonstration of this abnormal bronchus by the pathologist recalled to his mind a similar case which had occurred in 1939. A search of the records showed that this was the case of an infant, F.A., of 10 months, who began having attacks of cyanosis and dyspnoea at the age of 4 weeks. The child died in one of these attacks soon after admission to the hospital. Necropsy disclosed a grossly emphysematous right middle lobe which had herniated across the midline and occupied about one-third of the left side of the chest. The bronchus to the middle lobe was soft to palpation and on section showed an absence of cartilage in its wall.

Case 3. D.C., a girl, had a history of 'panting' since the age of 2 months, of bronchitis at 5 months and of poor development following this attack. She was thought to have a lung cyst and at the age of 17 months was subjected to lobectomy of the grossly distended right upper lobe. She made an uneventful recovery and a section of the upper lobe bronchus showed mural hypoplasia with almost complete absence of cartilage (Fig. 1).

Case 4. M.B., a girl, of 5 weeks, was admitted to hospital on June 27, 1953, during the height of an acute respiratory tract infection. A diagnosis of tension emphysema was made and an urgent operation to remove the left upper lobe was performed as her condition was deteriorating. She survived the operation but died six hours later. Examination of the specimen removed at operation showed that the bronchi after division were incompletely surrounded by cartilage but not entirely devoid of it. At necropsy the stump of the left upper lobe bronchus was sectioned and found to be deficient in cartilage. The bronchi to the other lobe were normal.

Case 5. T.M., a boy, had a history of cyanosis and difficulty in breathing 12 hours after birth. The symptoms continued and at the age of 4 months radiological examination suggested the presence of tension emphysema. The right upper lobe was removed in July, 1953, and he recovered from the operation. Examination of the specimen showed that the bronchus was deficient in cartilage and in all supporting structures. It was thought that the artery to the lobe was causing pressure on the bronchus and contributing to the obstruction. In other parts of the removed lobe some sections showed inadequate mural development while others showed the structure of normal bronchi.

These five cases have been reported previously (Nelson and Reye, 1954).

* A paper read at the meeting of the British Association of Paediatric Surgeons in London in July, 1956.

FIG. 1.—Section of affected bronchus in Case 3. There is only one small bar of cartilage seen in the section.

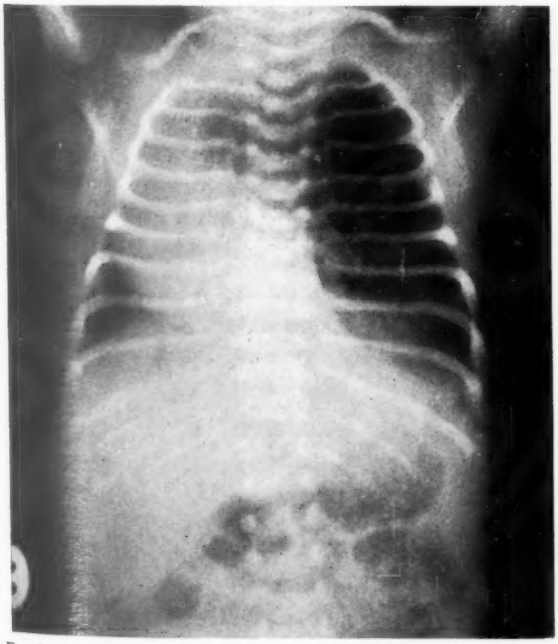

FIG. 2.—Emphysema of the left upper lobe with herniation across the midline in Case 6. Lung markings can be seen in the emphysematous lobe.

Case 6. The mother of J.C., a boy, had noticed a persistent wheeze from birth. At the age of 2 months he developed a respiratory infection and after this breathing became more difficult. He was admitted to hospital on September 6, 1953, at the age of 4 months after severe spasms of coughing causing cyanosis. Emphysema of the left lung with herniation of the lung into the right hemi-thorax was demonstrated by radiological examination (Fig. 2). He made a good recovery from this attack, but a considerable degree of mediastinal displacement persisted for some months, during which he was kept under observation. In May, 1954, the emphysematous left upper lobe was removed. Examination of the specimen did not disclose any cause of the obstruction, the bronchi being normal.

Case 7. D.B., a girl, was admitted to hospital on July 15, 1954, on the day of her birth. She was slow to breathe after delivery and cyanosed, and although her colour improved after removal of mucus by suction, she continued to have cyanotic turns. Her condition was improved by the administration of oxygen and she was kept in an oxygen tent. Examination of the chest showed that the right side moved less than the left, but breathing was very shallow. Radiological examination by fluoroscopy suggested that both lungs were emphysematous and that diaphragmatic movements were deficient. On July 16 radiographs suggested that both lungs were emphysematous, the left more so than the right, and on July 20 the same appearances were seen. Her condition continued to improve with the administration of oxygen and on July 29th further emphysema had occurred with mediastinal shift to the right. As there was no clear evidence that emphysema was confined to one lobe and as her condition continued to improve, it was thought wise to defer lobectomy. During the next two months her nursing care was a constant anxiety. She was tube fed for a considerable time as the effort of feeding exhausted her but gradually she was able to feed from a bottle, at first in the oxygen tent and later without this aid. By October she was in good condition and left thoracotomy was performed and an emphysematous upper lobe removed. The lower lobe was collapsed but inflated well at the end of the operation. The bronchus to the removed lobe was unduly soft and sections through the main bronchus and its primary divisions showed that they were supplied with cartilage but less liberally than is normal and quite large segments contained only small and immature cartilaginous bars.

On the day after operation mediastinal shift to the right was still present and a tension pneumothorax was aspirated. Two days later the mediastinum was central, the lower lobe expanded and she made an uneventful recovery.

Her subsequent history is interesting. In May, 1955, she was admitted to hospital again with cough and difficulty in breathing after a respiratory infection. Radiological examination showed well-marked emphysema of the remaining left lower lobe with mediastinal shift to the right. Since this period she has had five other attacks with wheezing and cough but they are less severe and she recovers rapidly.

Case 8. The birth of M.G., a boy, was normal but by the tenth day he had developed some cyanosis which persisted. He wheezed occasionally but had no alarming symptoms and progressed well. In August, 1954, when 1 month old, radiological examination showed emphysema of the right middle lobe with some mediastinal shift, and although he continued in good health further radiographs taken in January, 1955, showed that there had been a progressive increase in the degree of emphysema, which now produced more mediastinal displacement. On March 17, the right middle lobe, which was grossly emphysematous, was removed and he made a good recovery. Although the bronchus to the lobe was thin-walled the sections showed no abnormality in either the large or small bronchi or bronchioles.

The fact that in six of these eight cases the common pathological condition of diminution or absence of the cartilaginous support of the main bronchus to the lobe was found suggests that this is the essential cause of the condition. But in Cases 6 and 8, in which the emphysematous condition of the lobe was identical with that of the other cases, no abnormality was noted in the bronchi of the removed specimen. In Case 4 it was possible to examine both the lobe removed at operation and also the stump of the bronchus remaining. Although the deficiency was noted in the bronchi of the removed lobe it was even more apparent in the proximal bronchus. In other specimens it has been noted that there is an abrupt change from abnormal to normal bronchial structure in the more distal part of the lung, and it is suggested that section of the bronchus to remove an emphysematous lobe may be made through an area which is distal to the affected segment of bronchus, and that this may account for the failure to demonstrate the condition in the two cases.

All these children had symptoms from the neonatal period and in all cases a grossly emphysematous lobe was demonstrated producing mediastinal displacement. But there was a considerable variation in the severity of the symptoms and to some extent it is possible to correlate this with the pathological findings. In Case 1 the child died rapidly and there was a complete absence of cartilage in the bronchus. In other cases, in which small amounts of cartilage were present, the patients recovered from the acute condition and were cured by lobectomy.

That this abnormality of bronchial structure may be found in the presence of a much more benign condition is shown by the following case.

Case 9. S.I., a boy, was noted to have a persistent cough from the age of 6 months. He was subject to attacks of wheezing and had frequent attacks of bronchitis. He came under the care of Professor Dods at the age of 7 years when a radiological examination of the chest revealed appearances that were interpreted as being due to a cystic condition of the right upper lobe. A bronchogram was carried out and a large area in the upper half of the right lung field failed to fill with 'lipiodol' but crowded and compressed the upper lobe bronchi and to a lesser extent those of the middle lobe. The child was still suffering from cough and was dyspnoeic on slight exertion and unable to keep up with other children. In June, 1954, an emphysematous lobe was removed from the upper part of the right lung. This was an accessory lobe; its blood supply came from the artery to the upper lobe, but it did not show the gross degree of emphysema seen in the other cases. Examination of the specimen showed deficient cartilage in several of the bronchial branches. It was evident that there had been sufficient tension in this lobe to prevent the entry of 'lipiodol' when the bronchogram was performed, but not enough to cause herniation across the midline or mediastinal displacement which was a constant feature in other cases.

Discussion

A perusal of the literature shows that it has been common to mistake the condition of lobar emphysema for a tension cyst as was done in the earlier cases in this series, but a careful study of the radiographs will usually demonstrate fine lung markings through the affected area if one is alive to the possibility.

It has usually been found that the condition is confined to one of the upper lobes or the right middle lobe, but in Case 7 of this series there is definite evidence that the left lower lobe produced the typical picture of emphysema after the upper lobe had been removed, and it is not at all certain that there was not some degree of emphysema on the right side also.

Although the clinical picture is well recognized the method of its production is not so well established. In about half the reported cases a bronchial wall deficient in cartilage has been demonstrated. Various explanations have been put forward to explain the others. These include a flap of bronchial mucosa; a patent ductus overlying and compressing the bronchus; and abnormal flaccidity of the bronchial wall without absence of cartilage.

In the early neonatal period a grave emergency may arise as in Case 1. This raises the question as to whether any treatment is available to tide the patient over this period. In my case, under-water drainage through a needle gave no relief but more recently Korngold and Baker (1954) have treated two infants successfully by aspiration first of the affected lobe and later of the tension pneumothorax that resulted. Both these infants were relieved of the emphysema and had no recurrence in the next six months. It is difficult to understand how aspiration could relieve more than a lobule of the affected lobe unless the needle were introduced into a bronchus of some size, but the method offers some prospect of

tiding these infants over a dangerous period, although condemned by Sloan (1953) and others. Most writers are agreed that the only prospect of cure lies in removal of the affected lobe, and although there is no doubt that many of these infants may recover from acute attacks and aspiration may be a means of assisting this, there seems little place for conservative treatment when the lobe is permanently over-distended and produces mediastinal displacement over a long period.

In submitting the view that deficient cartilage formation is the underlying cause of the condition under discussion, I would set out the following considerations: (1) Deficient cartilage formation has been shown to be a direct cause of tension emphysema. (2) Deficiency may be of varying degrees; sometimes the deficiency is so great that the patient manifests symptoms immediately after birth. If the deficiency is of a lesser order some event such as an infection may produce mucosal changes and retention of secretion which will precipitate a crisis. (3) Sometimes, as we have found, the deficiency of cartilage varies in different parts of a bronchus. Here the possibility that tension emphysema will be caused is still present, but the cartilage deficiency may be hard to demonstrate in specimens removed at operation. (4) The demonstration of absence of supporting cartilage in the bronchus in a high proportion of cases would accord with my conception that this is the essential factor and the other abnormal conditions found are contributing causes.

I am grateful to my colleagues for referring cases, and to Mr. E. S. Stuckey for allowing me to include Case 5 in the series. Dr. Douglas Reye has been responsible for the pathological reports and has maintained a keen interest in the subject.

References

Korngold, H. W., and Baker, J. M. (1954). *Pediatrics*, **14**, 296.
Nelson, T. Y., and Reye, D. (1954). *Med. J. Aust.*, **2**, 342.
Sloan, H. (1953). *J. thorac. Surg.*, **26**, 1.

CONGENITAL LUMBAR HERNIA*

BY

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Although there is a substantial literature on the subject of lumbar hernia, a study of it discloses disagreement over interpretation of the terms 'congenital' and 'acquired' and, indeed, over the word 'hernia' itself. This confusion is by no means confined to lumbar hernia and it has been usual for the writers of the surgical classics of the nineteenth and early twentieth centuries to devote several paragraphs or pages to discussion of these three terms without agreement as to their precise meanings (Coley, 1910; DaCosta, 1931; Iason, 1941; Macready 1893; Ogilvie, 1937; Teale, 1846; Watson, 1948; Zimmerman and Anson, 1953). With respect to the more common abdominal hernias, such as inguinal and umbilical protrusions, the commonly accepted modern understanding is that, with the exception of post-operative incisional hernias, all hernias may in some measure be said to have a congenital origin.

While the material here to be recorded does not justify an exercise in semantics, it is pertinent to note that whereas nearly 200 cases of lumbar hernia have been reported, only a small fraction of this total, somewhere between 12 and 20 cases, have been accepted as being authentically congenital in origin. Authorities differ considerably over the criteria for acceptable cases, which accounts for uncertainty over the precise number on record, and it can only be said that they are extremely unusual.

Part of the confusion stems from the fact that most of the reported cases of lumbar hernia, at any age from infancy up, can be shown to be acquired. In the earlier literature violent external trauma or sepsis, either tuberculous or non-specific, were the common causes, and many of those in infants and young children were acquired in this manner. In more recent years sepsis has remained aetiologically prominent and to this has been added surgical trauma, such as removal of a section of the inner table of the ilium for bone grafting.

As late as 1950 Thorek reported two cases of lumbar hernia, both of traumatic origin, and collected and tabulated 124 additional cases from the literature. In the course of his review he said:

> 'I have not been able to find a satisfactory classification of lumbar hernia. Usually authors speak of a congenital type which is due to malformation or maldevelopment in the prenatal period, affecting muscles, aponeuroses, ilium, vertebrae, or lower ribs . . ., and an acquired type which is again subdivided into (*a*) spontaneous lumbar hernia, which is probably due to delayed effect of the conditions that produce the congenital type, aggravated by indirect injury from strain, obesity, extreme emaciation, hard physical labour, or other causes; and (*b*) traumatic lumbar hernia, which may be due to any one of a number of direct causes . . .'

The case to be presented here is unquestionably congenital in origin and is believed to be sufficiently unusual to merit publication. Comment on its embryological origin and on its anatomical and surgical characteristics will be included in the discussion that follows the case report.

Case Report

W.S. (C.H. No. 96002), a boy, now 28 months old, was observed at birth to have a large, soft, compressible mass in the left lumbar area, with palpable but inconspicuous deformity of the left lower ribs. The lesion caused him no apparent discomfort, and the only other obvious defect was an absent testis, also on the left. The mother's gestation had been normal and one sibling was healthy and free of congenital abnormalities.

The infant was referred for surgical consultation at 4 months of age, when enlargement of the mass had seemed to his parents to be disproportionately rapid as compared with his otherwise normal growth and development. Comparison of new radiographs with those taken at birth (Fig. 1) supported this observation and revealed, in addition to the costal deformities, hemivertebral defects of the lower dorsal and first lumbar vertebrae, with a compensated scoliosis that was not apparent in physical examination. In spite of the spinal anomalies, there was no neurological deficit. An apparent dextracardia was later disproved, and intravenous pyelography showed the position and function of the kidneys to be normal.

* Presented, in part, before the British Association of Paediatric Surgeons, London, July 18, 1956.

The infant was cheerful, well nourished and active (Figs. 2A and 2B), but because of progressive enlargement of the bowel-filled mass, early elective operation was advised and was performed on July 22, 1954. In Figs. 3A and 3B the dissection of the sac is shown, before and after it was opened. It was apparent at operation that both the superior (Grynfellt-Lesshaft) and the inferior (Petit's) lumbar triangles were affected. The muscles and fasciae forming the boundaries of these two triangles* were present, though somewhat distorted, with the exception of the latissimus dorsi which was not clearly demonstrated. An abdominal testis was found lying just within a snug internal inguinal ring, and Poupart's ligament and the inguinal canal appeared to be intact. The testis was left undisturbed.

* The lumbar area is bounded by the twelfth rib above, the iliac crest below, the erector spinae muscles behind and, in front, by a line from the tip of the twelfth rib to the iliac crest. This area is subdivided into the Grynfellt-Lesshaft (superior) triangle which is bounded by the twelfth rib and margin of the serratus posterior muscle, the posterior margin of the internal oblique, and the erector spinae muscles; and into Petit's (inferior) triangle, bounded by the latissimus dorsi and external oblique muscles and the iliac crest.

The fascial and aponeurotic margins were adequate for an effective imbricated repair which was constructed over linear closure of the peritoneal sac (Fig. 3C) after trimming off the redundant portion of the latter. Artificial re-enforcement with tantalum mesh or skin was found to be unnecessary.

Recovery was uneventful, and the patient left the hospital on the tenth day after operation. He remained well for three months but he then developed an inguinal hernia on the same side as the previous lumbar hernia, the repair of the latter remaining intact. At a second operation, the inguinal hernia was repaired and orchidoplasty was performed. The child has been examined at regular intervals during the 24 months since the first operation, without evidence of recurrence of either hernia, and the testis has remained in the scrotum, though slightly higher than its normal fellow on the opposite side. When the patient began to walk independently, a minimal scoliosis became clinically apparent and he was fitted with a light orthopaedic brace to prevent progression of the spinal curvature, but apart from this he has remained well (Fig. 4).

FIG. 1(A) Plain radiograph taken at birth. The bowel-filled mass in the left flank is well demonstrated. Hemivertebral defects are seen in the lower dorsal and first lumbar vertebrae. Supernumerary and fused ribs are present on both sides with distortion of the lower ribs on the left.

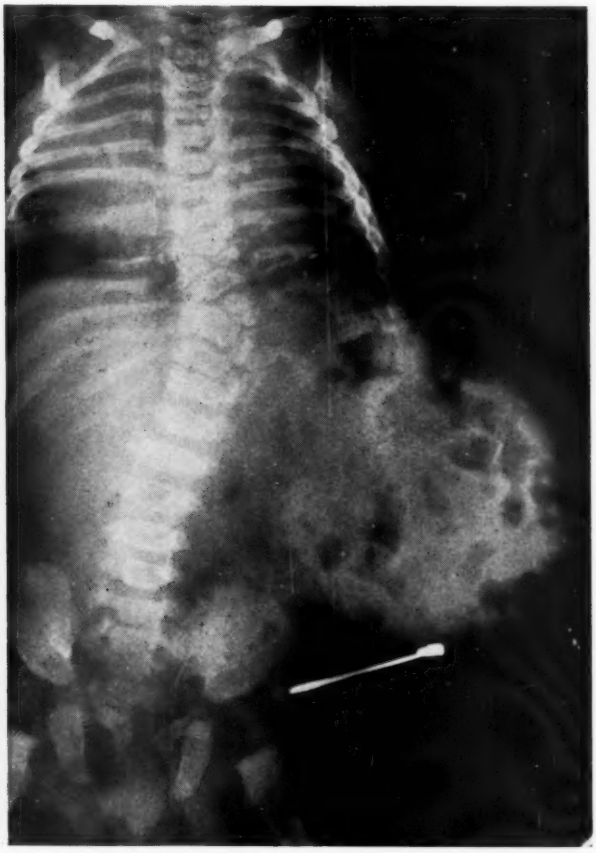
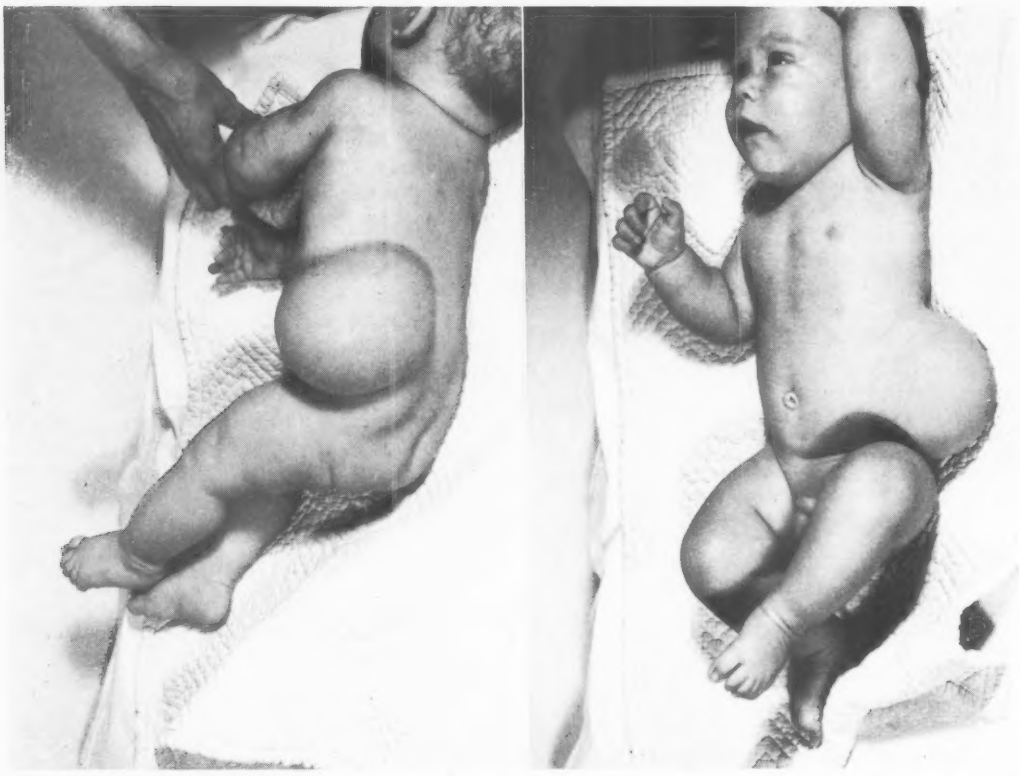


FIG. 1 (B).—Plain radiograph taken at the age of 4 months. The hernial protrusion has increased in size, out of proportion to the growth of the child.



2A 2B

FIG. 2 (A) and (B).—Photographs of the patient taken at the age of 4 months. The umbilicus is normal, and the protrusion is entirely in the lumbar region.

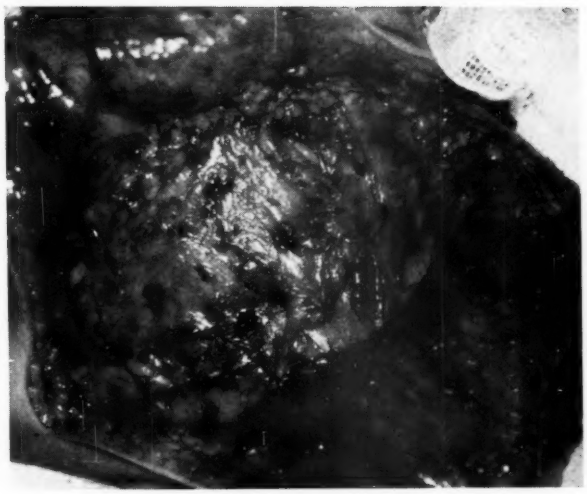
Pseudohernie (eigne Beobachtung).

FIG. 2 (C).—Reproduction of Borchardt's illustration of his case, reported in 1901.

Echte Lumbalhernie. (Fall von Wyss.)

FIG. 2 (D).—Reproduction of the illustration of Wyss' case of 1892. In his report a detailed anatomical dissection is described and illustrated.

3A 3B



3C

FIG. 3 (A).—Photograph of the dissection of the sac before it was opened. It was actually much thinner than it appears to be in the photograph. Convolutions of bowel can indistinctly be seen through the surface.

FIG. 3 (B).—Photograph of the sac after it was opened. The edge of the spleen is seen in the upper portion of the defect.

FIG. 3 (C).—Photograph of the completed repair before closure of the skin. This imbricated closure was constructed from available fascial structures, after previous linear closure of the sac in a separate layer.

FIG. 4.—Photographs taken 19 months after repair of the lumbar hernia. The period of post-operative observation has now been 24 months, without evidence of recurrence.

Discussion

Congenital lesions such as this are of interest from two standpoints, namely, the embryological mechanism which produces them, and the problem of effective surgical repair.

For the first consideration no conclusive answer can be given. The defect is plainly the result of a developmental accident that occurs much earlier than does omphalocoele, and which probably takes place during the third week of embryonic life. Nachod (1901) suggested that since the elbows of infants *in utero* rest on the lumbar area, the defect is produced by trauma to the mother, but this theory is not acceptable to modern embryologists. Monro, who is credited with the earliest description of congenital lumbar hernia (1802), is quoted by various authors as ascribing the defect simply to 'congenital defects of the abdominal wall'.

We have not been able, from material available to us, to trace the original description of Monro senior, which is credited to him by his son. The following is a translation from a footnote in Professor Braun's extensively documented discussion of the subject in 1879.

> 'This case of Monro is often cited, but never with an exact reference. I found the above report in A. Monro: *The Morbid Anatomy of the Human Gullet, Stomach and Intestines*, Edinburgh, 1811, p. 379, where the statement is made that this case was observed by the father of the author. There are probably still older reports of this case.'

Mastin (1890), whose patient had harboured the visible defect since birth, offered no embryological explanation, saying 'To account for three congenital cases (among 32 reports of lumbar hernia which he collected in 1890) is not possible, since there is nothing in the development of the abdominal wall to account for the formation of a gap in the lumbar region.' Modern students of developmental anatomy can do no better than to fix the time of the accident at a very early embryonic stage, and its precise mechanism remains unsolved (Patten, Warkany, Wilson, personal communications).

The remarkable thing is that a developmental error, whatever its nature, at such an early stage can result in such a comparatively small deformity, or group of deformities, in the full-term infant. The monstrosities of this region in stillborn infants, which Potter illustrates (Potter, 1952), are relatively easy to understand. She attributes them to abnormal cleavage in the mesoderm, between the amniotic sac and the wall of the blastocyst, but no acceptable data are available to explain what has gone wrong in the case reported here, or in others like it.

From the surgical standpoint, mild controversy exists. Borchardt (1901), whose illustration is reproduced (Fig. 2C), preferred to classify his case, which was very much like ours, as a 'pseudohernia'. Johnathan Macready, of Leeds, who also illustrated a similar case (1893), makes an arbitrary distinction between congenital lumbar hernia and 'congenital defect of the abdominal wall with bulging of the affected area'. As suggested earlier, such distinctions appear to us to be largely a matter of semantics. All three of these cases, Borchardt's, Macready's and our own, as well as that of Gage (1889), seem to us, after careful comparison of the definitions of many authorities already cited, to fall within accepted criteria for congenital lumbar hernia. The case described by Professor Wyss of Zurich in 1892 (Fig. 2D), for example, has never been challenged, although his patient harboured many more associated congenital anomalies than did ours, or the others we have mentioned. The deformities of the ribs and spine were almost identical with those demonstrated in our patient and the only difference, insofar as the hernia is concerned, seems to be that both the defect and the 'bulge' in Wyss's case were smaller than in ours.

It is impossible to describe a standard operation for the repair of these defects, because of the considerable variation in the degree and structural characteristics of the anomaly. Mr. Owen, of London, in 1888 repaired a lumbar hernia in a 5½-year-old girl without opening the sac, but this case was definitely the result of sepsis. The technique most frequently cited is that of Dowd

(1907) whose case was apparently congenital in origin, and in which the hernia was 'the size of a goose-egg'. He employed flaps from the aponeurosis of the gluteus maximus and latissimus dorsi muscles and, at the time of his report, eight months after operation, the repair remained intact in spite of a severe wound infection. On our case, although the defect was considerably larger, a flap from the gluteus maximus was not needed, and if the latissimus dorsi muscle was present, it was not recognized. It appears that the technique of repair must be improvised on the basis of the findings in the individual case. Needless to say, a strong overlapping reconstruction, employing available intrinsic fasciae and aponeuroses, is preferable to artificial splints such as tantalum mesh or skin. It is, no doubt, advisable to have these materials available, but they should only be used if a satisfactory repair is impossible without them.

Since this type of hernia is apparently so extremely uncommon, experience with it is usually limited to a single case, and constitutes a stimulating challenge to the surgeon who encounters it.

Summary

A case, believed to fulfil acceptable criteria for a diagnosis of congenital lumbar hernia, is presented, with a brief review of the literature and with comments on the embryological, anatomical, and surgical aspects of this unusual anomaly.

The senior author is greatly indebted to his co-author, Dr. Mattheis, for meticulous and painstaking translation of German reports, including the full text of Prof. Wyss' lengthy paper which was available only on microfilm; and to Miss Alice McCaffrey, Medical Librarian of the Cincinnati General Hospital, for her tireless efforts in tracing and making available original sources and texts.

References

Borchardt, M. (1901). *Berl. klin. Wschr.*, **38**, 1221, 1259.
Braun, H. (1879). *Arch. klin. Chir.*, **24**, 201.
Coley, W. B. (1910). In Keen's *Surgery*, ed. Keen, W. W. and DaCosta, W. C., Vol. 4, p. 17. Philadelphia and London.
DaCosta, J. C. (1931). *Modern Surgery*, 10th ed. Philadelphia and London.
Dowd, C. H. (1907). *Ann. Surg.*, **45**, 245.
Gage, Homer (1889). *N. Y. med. J.*, **50**, 650.
Iason, A. H. (1941). *Hernia*. Philadelphia.
Macready, J. F. C. H. (1893). *A Treatise on Ruptures*. London.
Mastin, C. H. (1890). *Ann. Surg.*, **12**, 20.
Nachod (1901). *Dtsch. med. Wschr.*, **27**, *Vereins-Beilage*, p. 172.
Ogilvie, W. H. (1937). *Post-graduate Surgery*, ed. R. Maingot, Vol. 3, p. 3597 (part XVIII). London.
Owen, E. (1888). *Brit. med. J.*, **1**, 957.
Patten, Bradley M. Personal communication.
Potter, Edith L. (1952). *Pathology of the Fetus and the Newborn*. Chicago.
Teale, J. P. (1846). *A Practical Treatise on Abdominal Hernia*. London.
Thorek, M. (1950). *J. int. Coll. Surg.*, **14**, 367.
Warkany, Josef. Personal communication.
Watson, L. F. (1948). *Hernia*, 3rd ed. St. Louis.
Wilson, James G. Personal communication.
Wyss, Oscar (1892). In *Festschrift gewidnet Theodor Billroth*, p. 1 (*Beitr. Chir.*). Stuttgart.
Zimmerman, L. M. and Anson, B. J. (1953). *The Anatomy and Surgery of Hernia*. Baltimore.

UROLITHIASIS IN CHILDHOOD

BY

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During the nineteenth and earlier centuries urolithiasis was a common paediatric problem and the many reports in the literature bear testimony to this. The total incidence of stone in the urinary tract has lessened in this country and at the same time there has been a disproportionate decrease in the number of cases seen in children so that the present incidence in childhood is low. However, urolithiasis must still be regarded as a problem with some paediatric significance, although, apart from relevant sections in special text-books, the recent literature on this subject has been limited to isolated accounts of individual cases. In order to obtain some idea of the present incidence of the disease a review of the clinical material of The Hospital for Sick Children was undertaken. At the present time stone in children not only differs in its incidence from that in the older reports but also in its character. Previously the condition was endemic and there were well-known 'stone-districts', such as Norfolk. Calculi were then predominantly found in the bladder and they were mostly composed of uric acid or urates. Not only are stones no longer endemic but those stones which do occur tend to be of different site and composition. It is also of interest to note that there does appear to be a difference in the nature of stone as it is seen in different localities. Thus in the non-endemic series reported by Winkel-Smith in 1944 a high percentage of stones was composed of calcium oxalate whereas in Meredith Campbell's cases the majority were composed of uric acid and urates. Stones are still common in many parts of the world and there the triad of endemicity, lower urinary tract calculi and stones composed of uric acid or urates still occurs.

During the past 20 years 85 children with urolithiasis were admitted to The Hospital for Sick Children, Great Ormond Street. There was no evidence to suggest that the stones were in any way endemic and they also conformed in other respects to recent reports in that the incidence was considerably higher in the upper than in the lower part of the urinary tract. Analysis of the stones revealed a high proportion of phosphatic calculi so that this series differs from both of those quoted above as well as differing in many respects from earlier reports. The comments which follow are based on the experience of these 85 patients who were all in-patients at some stage during the years 1936 to 1956. During the latter half of this period the total number of admissions to the hospital was 67,127 and during this 10 years 63 of the cases presented. The present relative incidence at The Hospital for Sick Children is thus approximately one case per 1,000 admissions, and, as world affairs considerably modified the figures for admissions during the first half of the period under review, the latter 10 years are more likely to be of present-day significance.

Classification

Although various methods of classification are available, including, for example, the anatomical situation of the stone, the age incidence, or the sex incidence, it would be preferable if all cases could be classified along aetiological lines. Unfortunately this is not yet possible and therefore it is probably better to recognize various clinical groups. To this end the 85 cases have been sub-divided into the following four groups:—

Group 1. Calculi occurring in the urinary tract in which there is an underlying congenital anomaly: there are 25 cases in this group and although it cannot be claimed that the congenital anomaly is the sole factor in these cases it seems reasonable to believe that it is the most significant in the production of the calculi.

Group 2. Calculi occurring in patients with errors of metabolism: there were nine such cases.

Group 3. Calculi resulting from other recognizable causes, of which there were five cases.

Group 4. Calculi due to unknown causes numbered 46 cases.

Table 1 summarizes this classification and also indicates the further nature of many of the cases and the sex incidence.

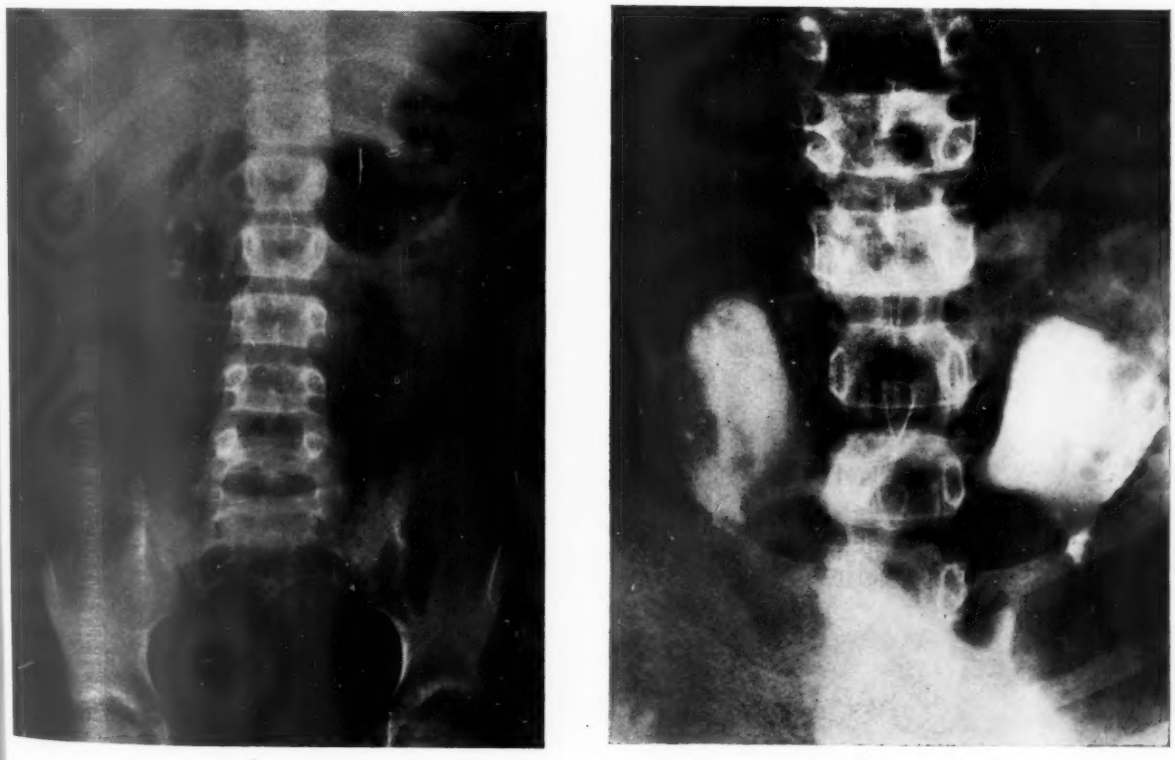
TABLE 1
CLASSIFICATION OF 85 CASES OF UROLITHIASIS IN CHILDHOOD

Group and Classification	No. of Cases	Males	Females
1. Congenital	25	17	8
Mega-ureter	10	6	4
Hydronephrosis	5	4	1
Ectopia vesicae and epispadias	7	5	2
Calyceal diverticulum	1	1	—
Crossed ectopia	1	1	—
Pyelon duplex	1	—	1
2. Metabolic	9	5	4
Cystinuria	5	4	1
Oxaluria	4	1	3
3. Other recognizable causes	5	3	2
Neurogenic bladder	2	—	2
Nephrocalcinosis	1	1	—
Recumbency	1	1	—
Foreign body	1	1	—
4. Unknown	46	27	19
Total	85	52	33

Clinico-pathological Features

Stone in the urinary tract may be symptomless, in which case its presence is only detected at operation, by incidental investigation, or at necropsy. Most cases do have symptoms, pain and haematuria being most frequently observed, but in addition to the passage of stones, the symptoms of infection and non-specific complaints are not uncommon. The children in this series had diverse clinical features and these were studied in each of the groups mentioned above, and at the same time the possible aetiological factors were considered in each case.

Group 1. Of the 25 cases which occurred in children with underlying congenital urinary abnormalities, five were associated with hydronephrosis. The symptomatology of this group was rather diverse but all the cases had in common a degree of pelvi-ureteric obstruction which would certainly have prevented the passage of the stones. Three of these cases were uninfected and one was completely symptomless, the stones being discovered in the course of investigation of splenomegaly (Fig. 1). In this, and in two of the other cases, the hydronephrosis was bilateral whereas the calculi were unilateral. In the four symptomatic cases the presenting complaints were abdominal pain in one, abnormal urine in the second, haematuria in the



1a 1b

FIG. 1.—Renal calculi in congenital hydronephrosis: plain radiographs and intravenous pyelogram. These calculi were symptomless and were incidentally discovered during the course of an investigation of splenomegaly.

third and symptoms of infection in the fourth, symptoms which can readily be attributed to hydronephrosis and not necessarily to stone.

In 10 of the cases the condition of mega-ureter was present. In three of these, there was stenosis of the lower end of the ureter, but in the others there was no such narrowing nor was there any evidence of extrinsic ureteral obstruction or infra-vesical obstruction. Even if one refers to the first three cases as examples of hydro-ureters, the remaining seven are best classified under the heading of mega-ureter. This group does not include any cases in which the ureteric dilatation was secondary to stone impaction or took the form of ureterectasis below pelvic or renal stones. In many of these cases the symptoms were those which might just as easily have occurred in similar cases uncomplicated by stones, although in three of the cases stones were passed spontaneously. Infection was present in eight of the 10 cases and there was a relatively high recurrence rate (four cases). At operation many of the calculi were very mobile and this, together with the multiplicity of the stones (Fig. 2) and the unspecific nature

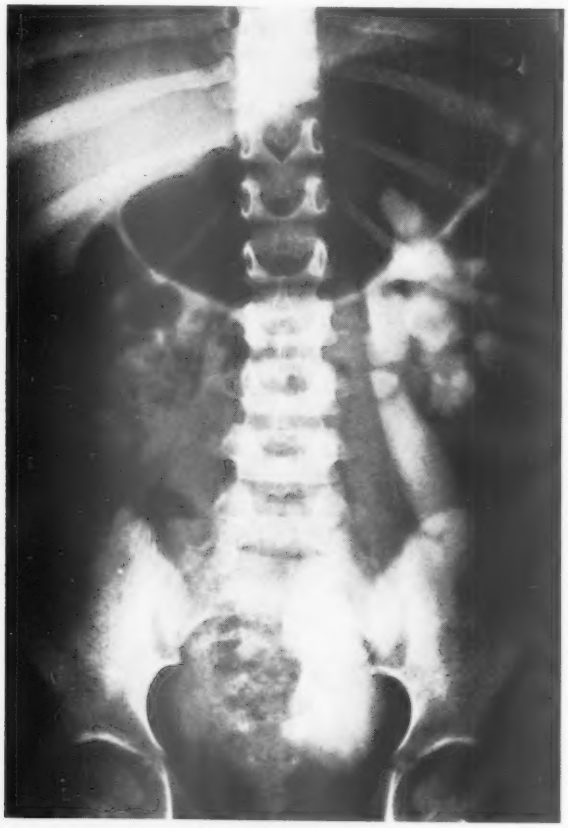


FIG. 2.—Multiple calculi in congenital mega-ureter: intravenous pyelogram in a girl who presented when aged 3 years with a history of cloudy urine.

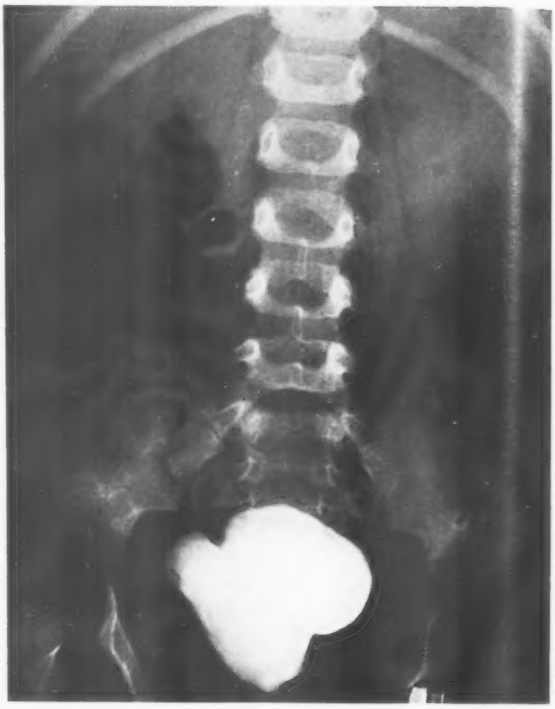


FIG. 3.—Vesical calculi in ectopia vesicae: straight radiograph showing stones in the reconstructed bladder. Symptoms included pain and attacks of straining.

of the symptoms, can be regarded as the main features of this particular group.

Three of the 'congenital' cases require but little mention. One case was associated with a calyceal diverticulum and this presented with the symptoms of infection. In the single case associated with a pyelon duplex there was persistent albuminuria while in the child with crossed ectopia haematuria was the initial complaint.

This leaves seven cases which were included in the first group. These seven were present in association with ectopia vesicae or epispadias and they therefore form a rather different group. This applies particularly to six of the cases in which the stones were found in the bladder or urethra following reconstructive surgery (Fig. 3). This group of cases is responsible for the highest percentage of vesical calculi in the entire series. This is certainly in marked contrast to the state of affairs in those series, both present and past, which are endemic in character. Pain and symptoms of infection were predominant in the six cases, although infection was not universal within the group. In four of these six cases with reconstructed lower urinary tracts, stones recurred, sometimes in the bladder, sometimes in the urethra and in one case a stone formed in the vagina.

In the seventh case in this group, a renal calculus followed the operation of uretero-colostomy.

With regard to the 'congenital' group as a whole, infection and stasis, separately or together, are the most significant factors in the pathogenesis of stone. This certainly applies to the cases with hydronephrosis, with congenital ureteric dilatation, and in this series to the case with a calyceal diverticulum and probably to the case with crossed ectopia. It is not possible to be certain about the case associated with pyelon duplex, although there, too, stasis may well have been a causal factor. In the reconstructed bladder, abnormal detrussor activity is likely to be a potent cause of urinary stasis.

Group 2. In nine of the series, an error of metabolism was detected, five of these being children with cystinuria and four were cases of familial oxaluria. The most obvious feature in this group was the absence of infection; in eight of the nine cases, the urine was sterile. Other features which were rather typical of this group included the presence of stones in the lower urinary tract (in four of the cases, two with vesical and two with urethral stones) and the fact that the stones were for the most part small. Their site and character tend to lead to the spontaneous passage of metabolic stones and this was described in two of the cases. Four of the cases had haematuria amongst their symptoms and in two of these this was the presenting complaint. There was a positive family history in three of the five cystinurics and all four oxalurics.

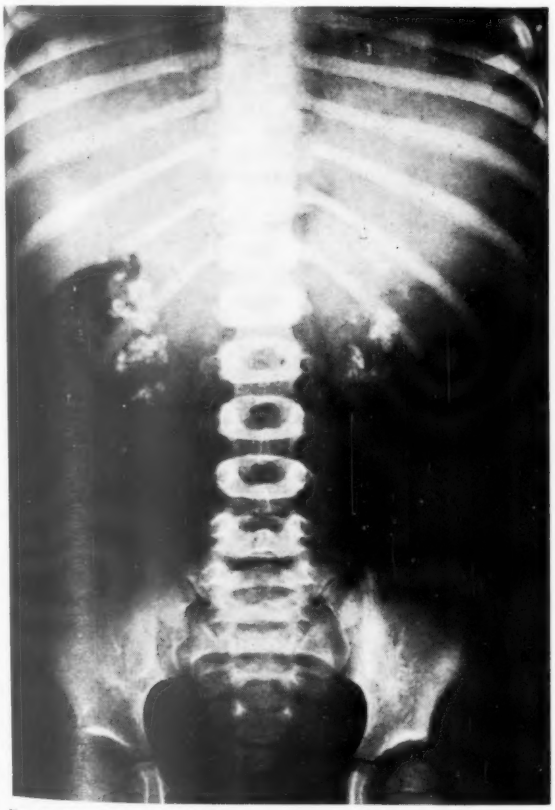


FIG. 4.—Familial oxaluria with nephrocalcinosis: plain radiograph of the abdomen in a child aged 2 years who had passed calcium oxalate stones in the urine five months' previously.

Familial oxaluria is a much less common condition than cystinuria and may be associated with diffuse renal calcification or calculus formation or both. Three of the cases in this series occurred in twin girls and their sibling brother. In one twin and the brother, haematuria was the presenting symptom, while the other twin was symptomless. The fourth case had a sibling with calculi and in addition had radiological evidence of nephrocalcinosis (Fig. 4). In this case, the oxalate excretion was demonstrated to be excessive. These cases of familial oxaluria are comparable to those reported by various writers, e.g., Aponte and Fetter (1954).

Group 3. These cases were grouped together for reasons of convenience and their clinical features are in no way remarkable. There was only one recumbency calculus in the series and this occurred in a boy with severe osteomyelitis. Haematuria was his presenting symptom. One patient had a foreign body calculus; the broken-off tip of a polythene catheter which had been previously inserted in the course of an operation on the rectum being the nidus. Incidentally, it is a little surprising that in the series there was no example of the not uncommon type of case, namely the girl with a vesical calculus surrounding a hair clip. Neurogenic disorders of the bladder were responsible for two of the cases; in one the calculus was found in the ureter, in the other in the kidney. The latter of these two ultimately died. The fifth case in this group was a baby with nephrocalcinosis; this diagnosis was made when the baby was aged 5 months, and seven months later calculi made their appearance in the left kidney and bladder.

The miscellaneous cases were really grouped together because the aetiological factors concerned were reasonably definite, but at the same time it was not possible to classify them with any of the other groups. In neurogenic disorders of the bladder, infection and stasis can be regarded as causal and similar factors can justifiably be invoked in the boy with osteomyelitis and recumbency calculi. The foreign body calculus does not present any real problem. The fifth member of this group is the case with nephro-calcinosis. Of the various causes of this condition, it seemed that infantile renal acidosis was the most likely basis in this case. This disease and allied metabolic disorders associated with

nephro-calcinosis are not uncommon in infancy and in the former nephrocalcinosis has been reported in about one-third of the total number of cases. The combination of nephrocalcinosis and calculi is, however, uncommon and there was only this one case of infantile renal acidosis in this series. It seems likely that an abnormality in calcium excretion was responsible for the formation of the calculus in this case; in fact it seems rather surprising that there was only one such case and that stones are not seen more frequently in infants suffering from this condition.

Group 4. In 46 of the cases, it was not possible to ascribe definite causal factors. These cases have, therefore, been grouped together, and at first sight this appears to be a large proportion of the entire series. Although this is so, unknown causes would be responsible for a larger proportion of cases in a comparable adult series. Infection was present in 35 members of this group and in many of these was responsible for the presenting symptoms. Haematuria was frequent, but stones were only passed spontaneously in seven, or possibly eight, of the group. A most interesting feature of this group was the predominance of stones in the upper reaches of the urinary tract and in only one of the 46 cases were the calculi confined to the lower urinary tract. Another feature was the high proportion of dendritic, staghorn and multiple calculi (Fig. 5), and in eight of the cases the calculi were bilateral. The presenting symptoms were extremely variable and included pain, failure to thrive, haematuria and abnormalities of the urine. It is the site and size of these calculi which distinguish them rather than their symptomatology. Thirty-six of the cases in this group had renal calculi, unilateral or bilateral, alone or in combination with calculi in the lower parts of the urinary tract. Of these, 36, 33 had infected urine, and it seems likely that infection may have played an aetiological role. However, in only one case could it be proven that infection definitely preceded calculus formation. There were four cases with sterile urine so that infection presumably played no part in the pathogenesis of those. The findings on analysis and the sex incidence of the cases are further evidence against a primary infective theory to explain these stones. Nine cases did not quite conform to this pattern in that the stones were smaller, were ureteric in site and behaved in a manner reminiscent of adult stones. In eight of these the urine was sterile, surgery was required in six, in two of the remainder the stones were passed spontaneously and in the other surgery was considered unnecessary. It seems highly probable that the latter group are of no special paediatric significance, whereas the large number of cases with large renal calculi are of much greater interest.

FIG. 5.—Renal calculi: plain radiograph of the abdomen of an 8-year-old girl investigated for pyuria. Nephrectomy was subsequently performed. Albuminuria was known to have been present since the age of 3 years so that earlier investigation may have avoided the necessity for nephrectomy.

The last case in the 'unknown' group had a vesical calculus and infected urine; there was a mild degree of hydronephrosis in one kidney so that it is probable that this stone originated in the upper urinary tract. Metabolic studies were carried out on many of these 46 cases but there was never any evidence to incriminate hypercalcaemia, hypercalcuria or abnormal phosphate metabolism as causal factors.

Age and Sex Incidence

There were 52 boys and 33 girls in the series. This male predominance extended to all groups, but was most marked in the larger groups. The age at which symptoms first appeared is shown in Table 2, which indicates that although the cases were seen throughout the period of childhood, the peak of incidence occurred in patients under the age of 4 years. Altogether 63% of the patients fall into this age group. A similar trend was observed by Winkel Smith in 1944 who reported 71 patients, 46 % of whom had symptoms before they were 4 years of age. The ratio of males to females in this series was 5 to 2. It may be argued that the age at which the first symptoms appeared does not of

necessity tell the age at which calculi were actually present. The symptoms may have preceded calculus formation or, on the other hand, the reverse could have occurred. The cases were particularly studied from this point of view, and there appeared little doubt that in most cases, if not all, the calculi had been present at least since the ages stated in Table 2.

TABLE 2
AGE INCIDENCE RELATED TO AGE OF FIRST SYMPTOMS

Group	Age of First Symptoms in Years		
	0-4	4-8	8 and Older
1	16	4	5
2	4	3	2
3	4	1	—
4	30	12	4

TABLE 3
AGE INCIDENCE RELATED TO AGE AT TIME OF DIAGNOSIS

Group	Aged 0-4 Years	Aged 4-8 Years	Aged 8 Years and and Older
1	11	6	8
2	4	3	2
3	2	3	—
4	25	11	10

TABLE 4
ANALYSIS OF THE 54 CASES UNDER AGE 4 YEARS

Age in Years	No. of Cases
0-1	9
1-2	16
2-3	18
3-4	11

Although diagnostic delay did occur it was not frequent as is seen by comparing Tables 2 and 3. Because such a high proportion of the patients were under the age of 4 years these younger cases were further analysed and the results are expressed in Table 4, which shows that in this series the maximum incidence was in the third year of life. Of the 18 cases which occurred during that year nine have been classified in the 'unknown' group.

Bacteriology

Infection was present in 60 cases (Table 5). The nature of the infecting organism can be seen in Table 6, and where more than one organism was present, the predominant one has been tabulated. Proteus was present in 60 % of the infected cases.

Site

Table 7 shows the situation of the calculi in the various groups. Cases classified as 'multiple' include stones in both kidneys, stones in both ureters,

TABLE 5
INCIDENCE OF INFECTION

Group	Infection Present	Infection Absent
1. Congenital	19	6
Hydronephrosis	2	3
Mega-ureter	8	2
Ectopia vesicae and epispadias	6	1
Calyceal diverticulum	1	—
Crossed ectopia	1	—
Pyelon duplex	1	—
2. Metabolic	1	8
3. Other recognizable causes	5	0
4. Unknown	35	11
Total	60	25

TABLE 6
ORGANISM IN 60 INFECTED CASES

Organism	No. of Cases
Proteus	36
Esch. coli	20
Staph. aureus	1
Strep. faecalis	2
Strep. viridans	1

TABLE 7
SITE OF CALCULI IN THE VARIOUS CASES

Site		No. of Cases			
		Group 1	Group 2	Group 3	Group 4
Kidney	Right	3	2	1	10
	Left	4	1	—	12
Kidney and Ureter	Right	1	—	1	5
	Left	1	—	—	3
Ureter	Right	1	—	—	3
	Left	4	—	—	3
Bladder		5	1	1	1
Urethra		1	—	—	—
Multiple		5	5	2	9

stones in both kidneys and one ureter, or both kidneys and both ureters, in one kidney and the contralateral ureter, or stones in both the upper and lower parts of the urinary tract.

Certain facts emerge from a study of Table 7. Thus in the 'unknown' group, 98 % showed stones in the upper urinary tract alone or in combination with stone in the lower urinary tract. Conversely only nine cases in the entire series had stones in the bladder or urethra alone, and of these six were cases with ectopia vesicae or epispadias, one was metabolic in origin and one was secondary to a foreign body in the bladder. Only one vesical calculus was met with in the cases with unknown aetiology. It seems therefore that in this non-endemic series of stones, bladder calculi were virtually unknown unless there was some special reason for their production. This is in marked contrast to older reports and to present-day reports of endemic series of stones, the latter being well exemplified by reference to Brown and Brown's report (1941) from Syria on this problem.

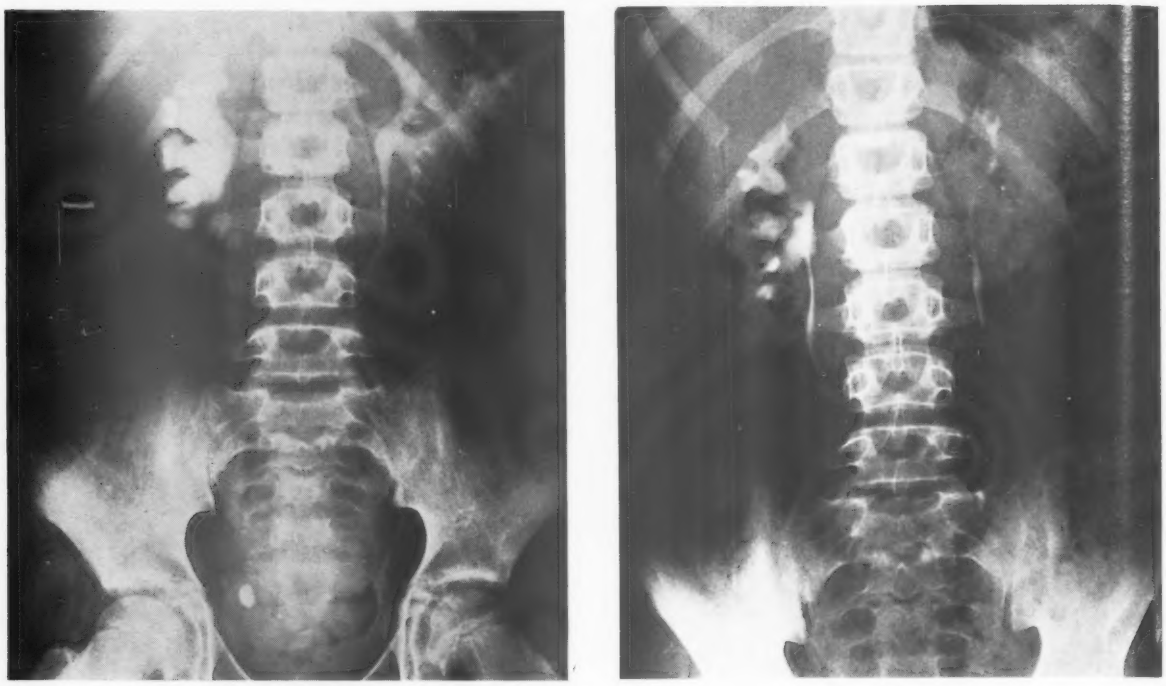


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FIG. 6.—Ureteric calculus: intravenous pyelograms before and two years after removal of the calculus showing reversible ureteric dilatation. The patient was aged 9 years and had suffered from attacks of abdominal pain and vomiting for 15 months.

Radiological Findings

All stones in this series were radio-opaque. Plain radiography was also used to follow the course of the disease after operation, and as will be seen later, is a useful adjunct to surgery. Intravenous pyelography was performed in many cases and was of considerable value in demonstrating anatomical abnormalities as well as giving some idea of renal function. One of the most important findings was dilatation of some part of the urinary tract, especially ureteric dilatation. In one group of cases the dilatation was primary and congenital, e.g., the cases of mega-ureters previously mentioned.

In a second group the dilatation was secondary to obstruction; ureteric stenosis was found in some cases. In others, stone in the ureter produced obstructive dilatation in the same way as this occurs under similar conditions in adults. Fig. 6 is an example of this type of problem; the figure shows serial radiography of a patient with a stone in the ureter. Originally it was thought that this represented a case of mega-ureter complicated by calculus formation, but ultimately it became apparent that there was no such underlying congenital abnormality.

In a third group, dilatation was seen below the calculi and in these it appeared that this was secondary (Fig. 7); the term 'ureterectasis' was employed to

FIG. 7.—Renal calculus with ureterectasis: intravenous pyelogram in a baby, aged 20 months with persistent urinary tract infection.

describe this finding. Considerable ureterectasis may be present and confusion as to the true diagnosis may readily result.

In some cases excretory pyelography was supplemented or replaced by retrograde pyelography. However, this latter procedure was only rarely necessary for purely diagnostic reasons.

Analysis

Calculi were analysed in 59 cases and the results are shown in Table 8. In many, organic material

TABLE 8
CHEMICAL ANALYSIS OF THE CALCULI

Substance	Group and No. of Cases			
	1	2	3	4
Phosphate (including Ca. Mg. NH_4 and CO_3)	13	—	4	19
Phosphate-uric acid	1	—	—	2
Phosphate-urate	1	—	1	1
Phosphate-oxalate	2	1	—	2
Phosphate-oxalate-uric acid (or urate-)	—	—	—	3
Phosphate-oxalate-cystine	—	—	—	1
Oxalate	—	2	—	—
Oxalate-carbonate	—	—	—	1
Cystine	—	5	—	—
No record of analysis	8	1	—	17

was found on analysis; however, it was not possible to correlate its presence or proportion with the presence or absence of infection. The most common finding was a phosphatic stone containing no trace of uric acid, urates or oxalates, and this occurred in 36 cases. The second most common finding was the pure cystine stone (five cases).

Treatment

One hundred and nine operations for removal of stone were performed in 77 of the cases, the discrepancy in the numbers being attributable to the cases with calculi in multiple sites and the cases with recurrence. The operative procedures (Table 9) consisted of simple removal of the stone alone (87

TABLE 9
109 OPERATIONS PERFORMED ON 77 CASES

Group	1	2	3	4	Total
Pyelo-lithotomy	5	1	—	19	25
Nephro-lithotomy	—	1	4	15	20
Pyelo-nephro-lithotomy	—	—	—	7	7
Uretero-lithotomy	6	—	2	14	22
Vesico-lithotomy	4	—	2	5	11
Urethro-lithotomy	1	—	—	1	2
Nephrectomy, nephro-ureterectomy, hemi-nephrectomy	4	2	—	16	22

operations) or removal of stone by excision of part of the renal tract (22 operations). Where indicated, corrective procedures on the urinary tract were carried out, e.g., pyelo-plasty, uretero-neo-cystostomy, lateral uretero-vesical anastomosis and bladder neck resection. Other operative procedures performed included drainage of a renal abscess. uretero-colostomy, pyelostomy and ureterotomy.

Of the eight cases which did not have any operative procedure, stones were passed spontaneously in five. Two of these were cases included in the 'unknown' group, the other three comprising one case of mega-ureter, one of ectopia vesicae and one case of familial oxaluria. The other three consisted of one patient awaiting operation, one with a small renal stone on whom surgery was not indicated, and one who died. This last was the only child in the series in whom death could be directly or largely attributed to the presence of calculi; he had multiple bilateral calculi and was admitted to hospital in a state of renal failure. The only other death in the series was a girl with a neurogenic disorder of the bladder who died as a result of the effects of back pressure and urinary infection.

Conservative methods of treatment included the use of the correct antibiotics and insistence on an adequate fluid intake. In the group with cystinuria, measures to alkalinize the urine were instituted and in one case with recumbency calculi 'aludrox' proved to be extremely efficacious.

Discussion

The diagnosis of urolithiasis in childhood should not present great difficulties and although the condition is now only seen infrequently, it is important that delay should not occur. Failure to recognize the condition may lead to chronic ill health and irreversible renal damage. Stone in the urinary tract is one cause of a diverse group of symptoms including those of urinary infection, haematuria and even physical retardation. Of these, the symptom which does merit particular stress is haematuria. Frank discoloration of the urine due to the presence of blood occurred in 35 cases, i.e., in over 40 % of the series. In 26, haematuria was the presenting complaint. In one, the initial diagnosis was ' angioma of the urethra' which must be one of the most infrequent conditions in childhood; in that patient nephrectomy was ultimately required and it appears almost certain that an earlier correct diagnosis might have prevented this necessity. Several cases were provisionally diagnosed as nephritis and several of these carried this label for rather long periods. Haematuria in an otherwise fit child calls for a full urological investigation and only in this way will diagnostic delays be avoided. As pointed out by Wyllie (1955) there are many causes of haematuria in

childhood, but its total frequency is not great and therefore all cases should be carefully investigated.

Should the symptoms arouse any suspicion that the child may have stone somewhere in the urinary tract, investigation should lead to early confirmation, This investigation should proceed along three lines, namely, radiographic, metabolic and bacteriological. A plain film of the abdomen is very readily obtained and there seems no reason why this should not be routine in all children showing haematuria, except those obviously suffering from acute glomerulonephritis, and all cases of urinary infection in boys and chronic or recurrent urinary infection in girls. It might well be added that if *Proteus* be shown to be present added suspicion should perhaps be aroused. With regard to abdominal pain, wholesale radiographic examination is certainly not to be advocated, but if there is anything to suggest that the pain may have an organic basis, then a radiograph will rapidly diagnose or exclude urolithiasis as the basis for the symptoms. Because the condition is now rare, investigation of suspected cases will often lead the clinician to some alternative diagnosis, and in any case it is important to note that although plain radiography is of considerable value, excretory pyelography is the more important requirement in the final analysis.

Metabolic investigation will only prove valuable in a limited number of cases. However, the urine should be examined to diagnose or exclude the condition of cystinuria and if familial oxaluria is suspected, the daily oxalate excretion should be estimated.

Metabolic investigation is not complete until the removed stone has been analysed because further facts of value may then be discovered. Serum calcium studies should be carried out to avoid missing any condition causing a generalized upset in the calcium metabolism.

The conditions which enter the differential diagnosis are numerous, but it is possible to group them as follows: first, other conditions affecting the urinary tract, e.g., nephritis, infection without stone formation and neoplasms of the kidney; secondly, other conditions producing similar symptoms, e.g., abdominal colic of intestinal origin, febrile attacks of infection elsewhere in the body; and thirdly, conditions responsible for intra-abdominal calcification, e.g. nephrocalcinosis, tuberculous mesenteric adenitis.

The application of the label urolithiasis to the case is insufficient. To this must be added the underlying cause and the assessment of the entire urinary tract. In other words, the diagnostic requirements form a triad, namely, the diagnosis of urolithiasis, the diagnosis of the underlying lesion (if possible) and the anatomical state of the urinary tract and total renal function.

Treatment requires but little discussion. Few cases can be managed conservatively and once diagnosed, operation is of 'urgent convenience'. Pre-operatively complete assessment of the renal tract is essential in order to make the correct decision regarding the nature of the operative procedure. In some cases, simple removal of stone will suffice, in others an underlying anomaly may require simultaneous correction and in a third group excision of part of the renal tract will be needed to satisfy the therapeutic requirements. Except in this last instance operative radiography is of considerable value and when nephro-lithotomy or pyelo-lithotomy has been performed, the exposed kidney should be radiographed using a suitable technique. In this way any calculi remaining can be detected and removed immediately. Post operative measures should follow routine urological practice, namely choice of the correct antibiotic, alkalinization of urine in the 'metabolic' group and insistence on an adequate fluid intake. Prophylactic treatment is particularly relevant in the patients with inborn metabolic disorders, and to this end, when a 'metabolic' stone is discovered, the urine of other members of the family should be examined and the correct treatment instituted where necessary. Another aspect relevant to prophylaxis concerns recurrence, which can best be avoided by complete pre-operative investigation, and, at the time of operation by correction of any underlying congenital anomaly and removing all calculous material.

In some of the 'unknown' groups a history of acute (non-urinary) illness in the early months or years was obtainable and it is possible that some metabolic upset at such a time was responsible for the early calculus formation. In regard to this suggestion, phasic hypercalcuria is one possibility, temporary dehydration is another. Although this must remain hypothetical in these cases it is interesting to speculate about a disease which has so obviously changed its character during the last 100 years.

Summary

Urinary stone in childhood in this country has changed its character. No longer is the disease endemic; calculi are not found predominantly in the lower urinary passages, nor are they mostly composed of uric acid or urates.

Eighty-five cases seen at The Hospital for Sick Children during the past 20 years have been studied and their features exemplify these changes. The cases were classified into four clinical groups, in the largest of which aetiological factors were indefinite.

Boys exceeded girls in the series (52 cases to 33) and the maximum incidence was during the third year of life. There was no significant discrepancy between the age at which symptoms first occurred and the age of diagnosis. In the cases with infected urine *Proteus* was the organism most commonly present. The significance of ureteric dilatation accompanying urolithiasis has been discussed and it was pointed out that the dilatation may be the cause (congenital mega-ureter) or the effect (ureteric obstruction due to calculus or ureterectasis) of stone.

There was a high proportion of phosphate stones, comprising 61 % of the cases in which stones were analysed. Haematuria is a very frequent symptom and demands thorough investigation. In the series there was a definite relationship between age, sex and chemical analysis of the stones, and it is suggested that this relationship may be of some aetiologica significance.

It is a pleasure to express my thanks to Dr. D. I. Williams, genito-urinary surgeon to The Hospital for Sick Children, who originally suggested this study and whose advice and help were a constant stimulus. My thanks are also due to members of the consultant staff for permission to study their cases and to Mr. D. Martin for the preparation of the photographs. I also wish to express my indebtedness to the X-ray and Records Departments for their help.

References

Aponte, G. E., and Fetter, T. R. (1954). *Amer. J. clin. Path.*, **24**, 1363.
Brown, R. K., and Brown, E. C. (1941). *Surgery*, **9**, 415.
Winkel Smith, C. C. (1944). *Acta. chir. scand.*, **90**, 1, 179.
Wyllie, G. G. (1955). *Proc. roy. Soc. Med.*, **48**, 1113.

THYROID CARCINOMA IN CHILDHOOD IN GREAT BRITAIN

BY

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Carcinoma of the thyroid in childhood is a rare condition, and after an extensive search only seven cases have been found in Great Britain.

In 1920 Hughes dissected enlarged cervical glands in a 13-year-old girl; the glands were found to be invaded by papilliferous thyroid carcinoma and thyroidectomy was done. The child was well three months later.

Moncrieff and Poynton (1929) reported the case of an 11-year-old girl who had had a swelling of the neck since the age of 4, with recent enlargement and respiratory obstruction. Removal was attempted but the child died; post-mortem examination showed a carcinoma of the thyroid, partly solid and partly papilliferous, and infiltrating the trachea.

Taylor and Wilkinson (1935) reported a 6-year-old girl who had a cough for five weeks, dyspnoea, but no haemoptysis, after a cold. There were small, discrete, hard cervical glands, and a radiograph of the chest showed appearances suggestive of miliary tuberculosis but the Mantoux reaction was negative. During the next two months the glands enlarged and fused, producing stridor, increasing dyspnoea from tracheal compression and eventually death from asphyxia. Post-mortem examination showed a partly solid, partly papillary carcinoma of the thyroid, infiltrating the trachea and invading the cervical glands. The lungs were studded with metastatic deposits.

d'Abreu (1936) treated a girl of 16 who had had a swelling in the neck associated with a 'choking' feeling for three months; biopsy of a gland in the left anterior triangle showed infiltration with adenocarcinoma. Subsequently left hemithyroidectomy and dissection of the remaining glands was done, and when seen nine years later she was married, with a family, and had had no recurrence.

Joll (1936) removed an adenocarcinoma of the thyroid in a 16-year-old girl. Three courses of radiotherapy, with a total dose of 2,400 r on each occasion, were given and she has remained well.

Goldie (1950) examined an operation specimen from a 12-year-old boy; he had had a swelling of the thyroid excised one year before, and the swelling had recurred. The gland was greatly enlarged and both lobes contained multiple nodules; some of these were composed of undifferentiated epithelial cells, some showed papillary structure and others mixed solid and papillary elements. Atypical cells and mitoses were found towards the periphery of the nodules.

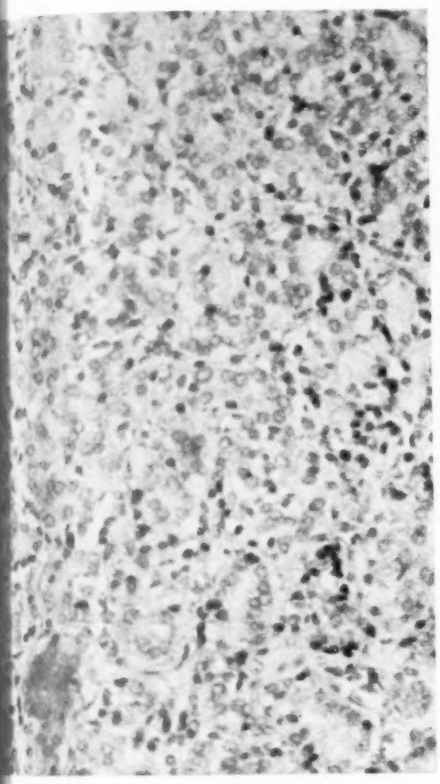
East (1954) treated a 14-year-old girl who had had a large gland in the left upper cervical chain for four years; the gland was excised and shown to be infiltrated with papillary adenocarcinoma. Subsequently total thyroidectomy was done, and the left lobe contained a papillary and tubular colloid-secreting adenocarcinoma. Professor Smithers subsequently investigated her with radioactive iodine but found no reason for treating her with it. Three months after operation enlarged cervical glands were found and removed from both sides. Two months later enlarged supraclavicular glands were noted, and Professor Smithers gave a course of radiotherapy, 3,700 r in 39 days. The child has since remained well, with no recurrence after one year.

Winship and Chase (1953), have commented on the paucity of reported cases of carcinoma of the thyroid in children in western Europe, and could collect only 42. Winship (1951) also indicated that inadequate follow-up and deficient hospital records hinder the evaluation of therapy for a condition of high mortality in children, emphasizing the importance of early diagnosis and the radical removal of all nodular goitres. It is therefore felt that the following case should be recorded.

Case Report

S.L., a boy of 9 years, was congenitally deaf and had been having speech therapy for five years. A swelling of the neck had been noticed for two years, but his mother did not seek advice until tonsillitis one month previously had seemed to cause an increase in the size of the swelling.

FIG. 1.—Adenomatous area of thyroid.
FIG. 2.—Adenocarcinomatous nodule of thyroid.



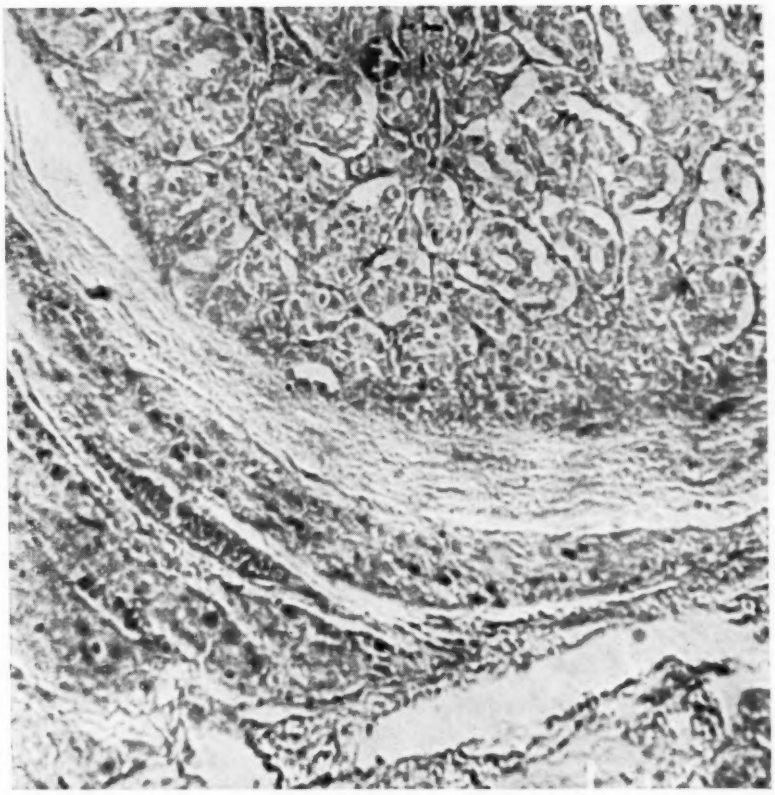
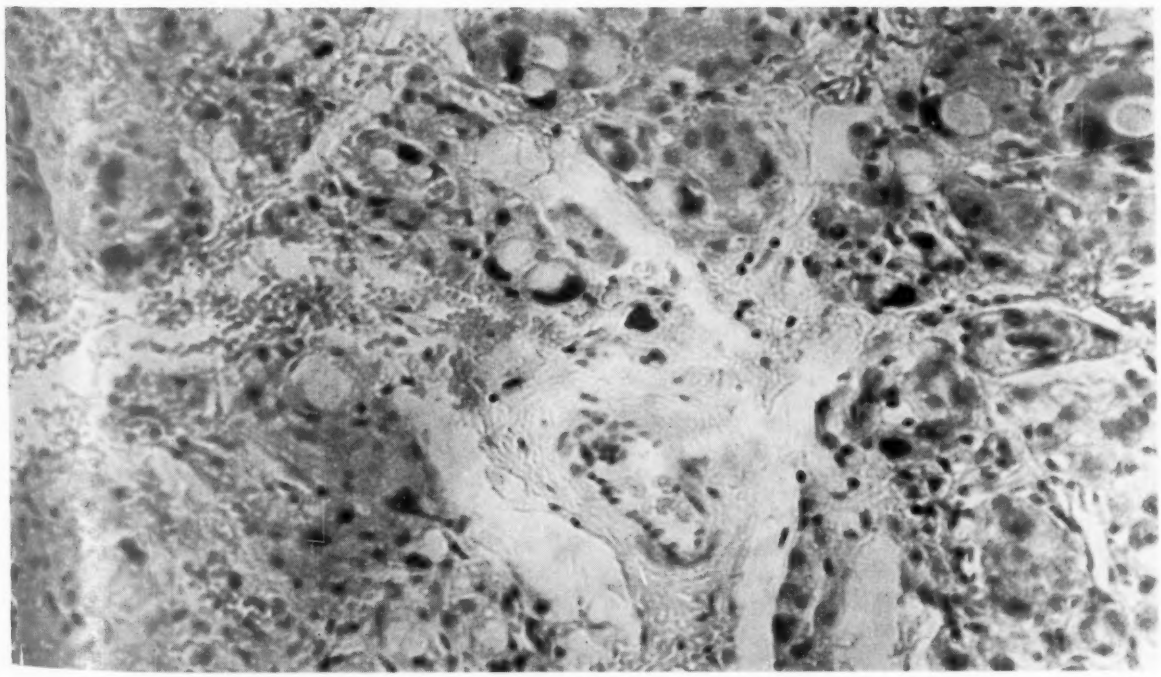


FIG. 3.—Adenocarcinomatous area of thyroid.



The boy's respirations had become noisy and he tired easily.

There was a diffuse, nodular swelling, 4 cm. by 3 cm., in the left lobe of the thyroid gland, with a solitary nodule, 1·5 cm. in diameter, in the isthmus. The right lobe was slightly enlarged but was not nodular. The swellings felt cystic. The lymph nodes were not enlarged and there were no signs of toxicity. It was decided to explore the swelling.

On August 21, 1952, under endotracheal nitrous oxide, oxygen and ether anaesthesia, the thyroid was explored through the usual collar incision with division of the left infrahyoid muscles. The pyramidal lobe contained a cyst, and the left lobe contained numerous small hard nodules with one larger cyst. The right lobe contained a few small nodules. As the nature of these was still in doubt, most of the left lobe was removed, about one-quarter being left, and the pyramidal lobe and most of the isthmus were also excised.

Pathological Report. The specimen was a lobe of thyroid gland, 4·75 by 2·5 by 1·5 cm., pink and soft. On the cut surface several sharply demarcated yellowish-pink nodules, 1-1·5 cm., in diameter, were seen, together with a pea-sized cyst lined by smooth, white membrane.

Histology. Three different types of tissue were present: (1) Normal thyroid tissue with slight papilliform proliferation of the epithelium; (2) tissue consisting of solid cords of cubical or low columnar cells with a vesicular nucleus and an abundant vacuolated cytoplasm, and vesicles with a minute lumen and a lining of similar cells. In this area were groups of smaller cells with dark nuclei (Fig. 1); (3) solid cords of cells, larger than those in area (2), with large nuclei varying in shape, usually hyperchromatic, sometimes multiple, and small vesicles lined by the same type of cells. Mitoses, sometimes atypical, were not uncommon in this area (Figs. 2 and 3).

The cyst was lined partly by tissue of type (2), partly by fibrous tissue with a patch of calcification, and neoplastic tissue of type (2) and (3) was present within the capsule.

The findings were consistent with the diagnosis of adenocarcinoma of the thyroid. Accordingly, the chest and long bones were radiographed, but no secondary deposits could be seen.

Second Operation. On August 28, under endotracheal nitrous oxide, oxygen and ether anaesthesia, the wound was re-opened and the infrahyoid muscles divided. The recurrent laryngeal nerves were dissected and preserved, and the right lobe with the remains of the left lobe and the isthmus removed.

The macroscopic and histological appearances were the same as in the previous specimen.

The boy was referred to Mr. W. H. Bond at the Queen Elizabeth Hospital, Birmingham, for radiotherapy. He was given tracer dosage only of 250 micro-curies of I^{131} on September 8, 1952. One hundred per cent. of the dose was excreted and no residual activity was found to Geiger counting. Subsequently a course of radiotherapy was given by simple opposed fields of a central dose of 3,000 r in 15 treatments over three weeks, with insignificant reactions.

The boy has been followed up as an out-patient and has remained well on a maintenance dose of 8 grains of thyroid weekly. When last seen in May, 1956, the growth had not recurred.

Comment

Taylor and Wilkinson (1935) stated that on clinical grounds thyroid carcinoma in childhood could be divided into two groups, namely (1) relatively benign, slowly growing tumours, without infiltration or glandular invasion. The diagnosis as a rule was made histologically, and the appearances were those of a malignant adenoma. (2) Rapidly growing tumours with early invasion of the neck tissues, trachea and lymph nodes, and distant metastases; histologically the appearances were those of papilliferous adenocarcinoma.

Winship (1951), in an extensive review of cases in childhood, found 93 reported in the literature, added four of his own, and collected 95 further unpublished cases from various centres of North America. The first sign of disease in most cases was a painless lump in the neck, usually in the thyroid gland, but occasionally in its lymphatic drainage area. Few children had symptoms of advanced thyroid carcinoma, e.g., dysphagia or dyspnoea. The patients in his series had treatment varying from surgery alone to radiotherapy alone. Fifty-three per cent. had surgery supplemented by radiotherapy. A sufficient time has not yet elapsed for the various forms of treatment to be evaluated, but he felt that the first operative treatment, if sufficiently radical, offered the best chance of cure.

Summary

Reports of thyroid carcinoma in children in Great Britain are reviewed, and the case is described of a boy of 9 years, treated by total thyroidectomy and radiotherapy, alive and well three years and nine months after operation. The clinical features of such tumours are briefly discussed.

I am indebted to Mr. R. K. Debenham for permission to treat this child and publish the report, and to Mr. W. H. Bond for the post-operative radiotherapy. My thanks are also due to Dr. Frances Braid for her assistance in stabilizing the thyroid dosage, to Dr. H. S. Baar for the pathological examination and to Mr. J. G. Williamson for the photography.

References

d'Abreu, A. L. (1936). Personal communication.
East J. A. (1954). Personal communication from Mr. J. A. East and Dr. J. W. Whittick.
Goldie, W. (1950). Personal communication from Dr. Georgiana Bonser.
Hughes, B. (1920). *Brit. med. J.*, **1**, 362.
Joll, C. A. (1936). Personal communication from Mr. A. H. Hunt and Dr. J. W. Whittick.
Moncrieff, A. and Poynton, F. J. (1929). *Proc. roy. Soc. Med.*, **23**, 109.
Taylor, A. B. and Wilkinson, B. M. (1935). *Archives of Disease in Childhood*, **10**, 99.
Winship, T. (1951). *Trans. Amer. goiter Ass.*, p. 364.
—— and Chase, W. W. (1953). *Arch. chir. neerl.*, **5**, 253.

TREATMENT OF PORTAL HYPERTENSION IN CHILDREN*

BY

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Bleeding oesophageal varices in association with splenomegaly are a serious syndrome highly suggestive of portal hypertension. Blakemore and Lord (1945) and Whipple (1945) described a successful method of treating the condition: they short-circuited the congested portal flow directly to the caval system. This method opened up a possibility of treating portal hypertension in children. Of our own 82 patients operated upon because of portal hypertension, 33 were below 20 years of age. The material is classed according to age and site of the portal block in Fig. 1, from which it is apparent that in childhood the block was most frequently extrahepatic, while intrahepatic block, which was usually seen in patients with liver cirrhosis, was most common between the ages of 40 and 60 years.

Splenoportography and measurement of the intrasplenic pressure proved useful in the establishment of a pre-operative diagnosis in both children and adults. Splenoportograms of children with portal hypertensions are given in Figs. 2 and 3 and typical radiographs with intra- and extrahepatic block in Figs. 4 and 5. The main indication for surgical intervention was oesophageal haemorrhage. The purpose of treatment was to reduce portal hypertension and thereby the tendency to oesophageal haemorrhage by the establishment of a shunt between the portal and the caval systems.

Intrahepatic Block

Of eight patients with intrahepatic block, an anastomosis was established in seven (Fig. 6). In the eighth only splenectomy was possible. Of these seven patients, one died three years later in hepatic coma. Post-mortem examination revealed a patent spleno-renal anastomosis at least 1 cm. in width. In one patient oesophageal haemorrhage recurred about a fortnight after the operation for which reason a direct portacaval shunt was established after a further 14 days. Oesophageal bleeding did not recur during the following 20 months, that is, until August, 1956, when the patient died from necrotising liver cancer which might have been due to malignant degeneration of the primary disease, cirrhosis of the liver. The anastomosis was perfect. The other five patients have been symptom-free for one to seven years.

* A paper read at the meeting of the British Association of Paediatric Surgeons in London in July, 1956.

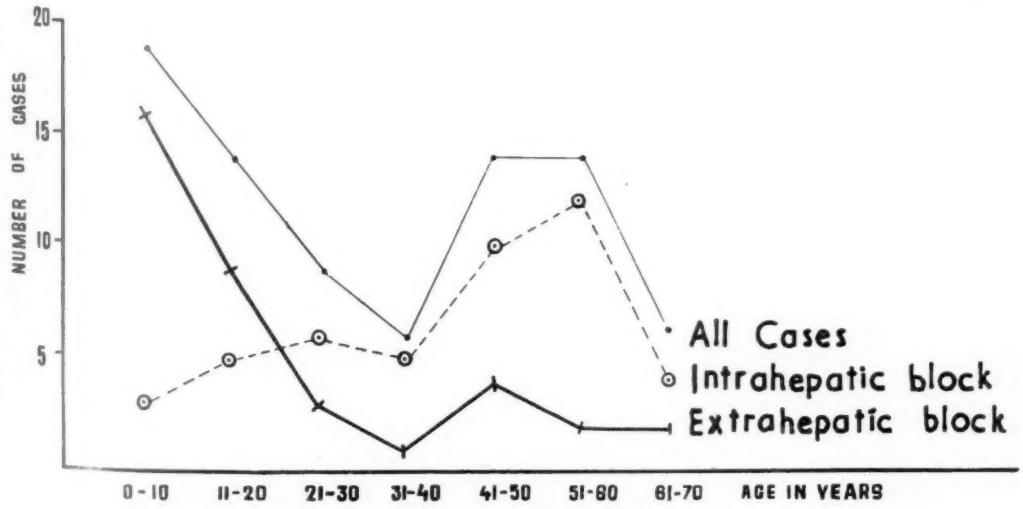

FIG. 1.—Location of portal block at different ages.

FIG. 2 (A).—Intrahepatic block, with occluding thrombus in the portal vein. Note the flow of blood through the collaterals.

FIG. 2 (B).—The same case after portacaval anastomosis. The blood flow through the collaterals has ceased.

FIG. 3.—Portal hypertension with extrahepatic block. A collateral stricture is seen in the hilum of the liver.

FIG. 4.—Portal hypertension due to intrahepatic block. Narrow vessels in the liver. Extensive collaterals.

FIG. 5.—Extrahepatic block due to thrombosis of the splenic vein.
FIG. 6.

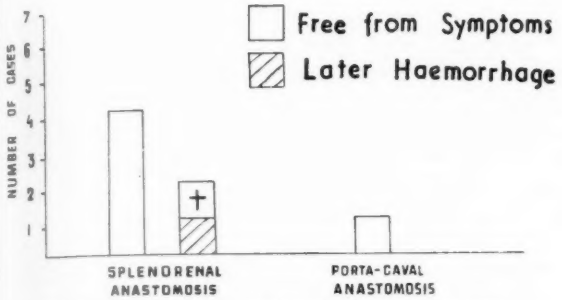

FIG. 6.—Distribution of intrahepatic block in seven cases.

Extrahepatic Block

Not Previously Splenectomized. This group consisted of 21 patients, aged 2-20 years (Fig. 7). After spleno-renal anastomosis haemorrhages recurred in nine. Of these, bleeding was fatal in six. The remaining nine have since been symptom-free (follow-up one to four years). In the two patients in whom spleno-renal anastomosis was established (vitallium tube) haemorrhages recurred.

Previously Splenectomized. The surgical results obtained in patients who had previously been splenectomized, including those who had had recurrent haemorrhages after spleno-renal anastomosis, are given in Fig. 8. All of the six patients in whom an anastomosis had been established had haemorrhagic recurrences. Direct attack upon the oesophageal varices, i.e., intra-oesophageal division of varicose veins or partial oesophago-gastrectomy appeared to give more encouraging results. Of the six patients treated in this way, only one had a recurrence. In three of these cases the follow-up period is as yet only one year, and therefore not long enough to say anything definite about the prognosis.

The results thus show that half of the patients with extrahepatic block and treated by the establishment of a spleno-renal anastomosis had recurrences, while the results achieved in patients with intrahepatic block were somewhat more favourable. In patients who had previously undergone splenectomy, only six out of 17 were symptom-free one year after the operation.

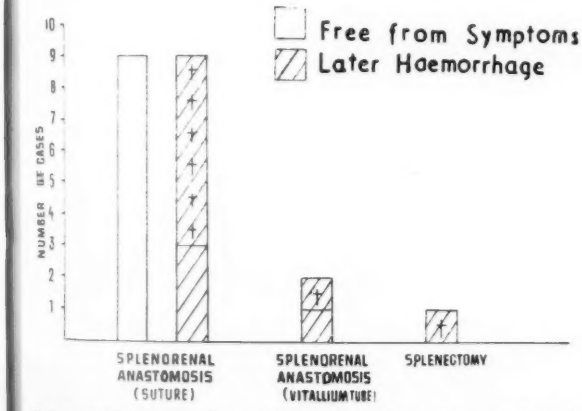

FIG. 7.—Distribution of extrahepatic block (not splenectomized) in 21 cases.

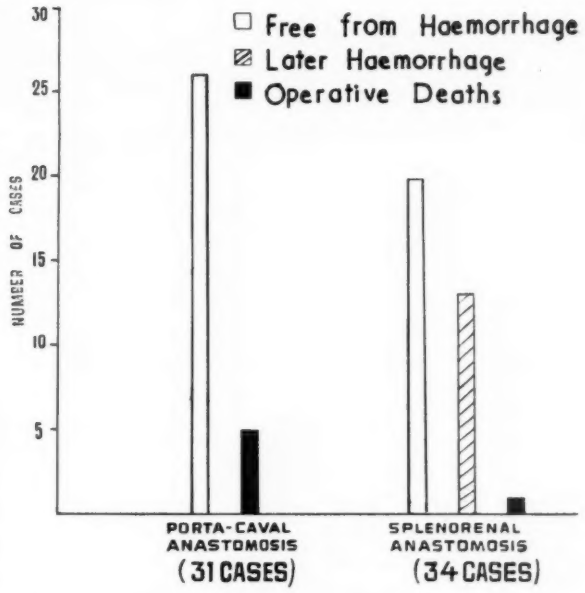

FIG. 9.—Results of portacaval and spleno-renal anatomosis.

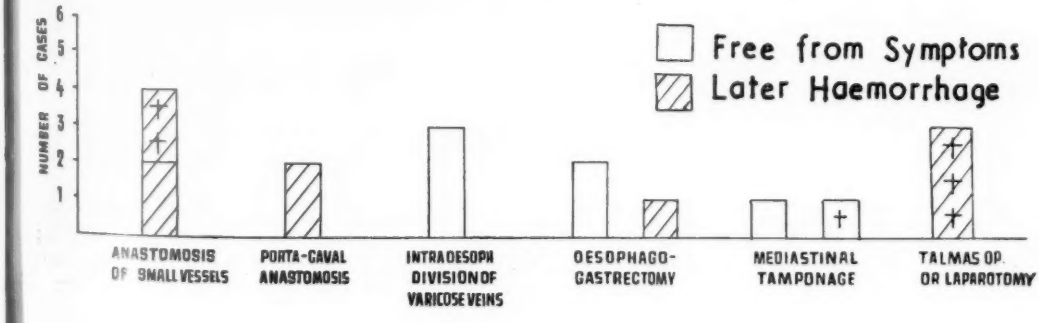

FIG. 8.—Distribution of extrahepatic block (splenectomized in 17 cases.

It is thus apparent that the primary mortality was higher in the group with intrahepatic block, but that the tendency to recurrence was considerably higher in the group with extrahepatic block, especially in the subgroup in which the patients had previously undergone splenectomy.

Fig. 9 shows the results of portacaval anastomosis and spleno-renal anastomosis achieved in the entire material, i.e., including adults. After portacaval anastomosis, all of the 26 patients who survived were free from recurrences, while 13 of 33 survivals after spleno-renal anastomosis had recurrences. The more favourable results of portacaval shunt can be explained (at least in part) by the fact that the lumen is larger and therefore involves less risk of occlusion than spleno-renal anastomosis, since we have been able to show that anastomosis large enough to relieve portal hypertension will control the tendency to recurrent oesophageal haemorrhage. In the treatment of portal hypertension in children the problem is to find a vessel wide enough to permit anastomosis for reducing portal hypertension without undue risk of subsequent occlusion. This might be achieved by the method recommended by Clatworthy, Wall and Watman (1955), i.e., division of a caval vein just above the bifurcation and anastomosing it end to side with a portal vein at its origin. A combination of the division of the vessels up towards the oesophageal region and a spleno-renal anastomosis might produce good results. Such a procedure should conduct more blood through the anastomosis and thereby possibly decrease the risk of occlusion.

REFERENCES

Blakemore, A. H. and Lord, J. W., Jr. (1945). *Ann. Surg.*, **122**, 476.
Clatworthy, H. W., Jr., Wall, T. and Watman, R. N. (1955). *A.M.A. Arch. Surg.*, **71**, 588.
Whipple, A. O. (1945). *Ann. Surg.*, **122**, 449.

PAEDIATRIC SOCIETIES IN THE BRITISH ISLES

The following is a list of paediatric societies and their principal officers at the time of compilation. Alterations when they occur, information on new societies or any omissions from this list should be passed to the Secretary of the British Paediatric Association.

I: National

British Paediatric Association
President: Professor John Craig
Secretary: Dr. P. R. Evans
Institute of Child Health,
The Hospital for Sick Children,
Great Ormond Street,
London, W.C.1.

The Royal Society of Medicine, Section of Paediatrics
President: Dr. D. V. Hubble
Secretaries: Dr. C. W. Kesson
Dr. T. P. Mann
The Royal Society of Medicine,
1, Wimpole Street,
London, W.1.

The British Association of Paediatric Surgeons
President: Denis Browne, Esq., F.R.C.S.
Secretary: R. B. Zachary, Esq., F.R.C.S.
Children's Hospital,
Sheffield.

The Scottish Paediatric Society
President: Professor John Craig
Secretary: Dr. J. H. Hutchison
Royal Hospital for Sick Children
Yorkhill,
Glasgow, C.3.

Scottish Surgical Paediatric Club
President: Matthew White, Esq., F.R.C.S.(Ed.), F.R.F.P.S.G.
Secretary: Wallace M. Dennison, Esq., M.D., F.R.C.S.(Ed.), F.R.F.P.S.G.
13, Ashton Road,
Glasgow, W.2.

Paediatric Pathology Club
Secretary: Dr. J. L. Emery,
Children's Hospital,
Sheffield.

Ulster Paediatric Society
President: J. S. Loughridge, Esq., F.R.C.S.
Secretary: Dr. W. A. B. Campbell
19, Adelaide Park,
Belfast.

Irish Paediatric Association
President: K. M. Maughan, Esq., M.B., B.Ch.
Secretary: Dr. Raymond Rees
18, Fitzwilliam Square,
Dublin.

Welsh Paediatric Club
Secretary: c/o Professor A. G. Watkins
Department of Child Health,
Llandough Hospital,
Penarth, Glam.

II: Regional

South West Paediatric Club
President: Professor A. V. Neale
Secretary: Dr. John Apley
Children's Hospital,
St. Michael's Hill,
Bristol, 2.

The Liverpool Paediatric Club
President: Professor N. B. Capon
Secretary: Dr. R. McL. Todd
Department of Child Health,
Alder Hey Children's Hospital,
Eaton Road,
Liverpool, 12.

Paediatric Society of the South-East Metropolitan Region
Chairman: Dr. R. C. Mac Keith
Secretary: Dr. S. D. V. Weller
50, Southborough Road,
Bickley, Kent.

The Aberdeen Child Health Society
President: Professor John Craig
Secretary: Dr. Norman C. Clark
374, Great Western Road,
Aberdeen.

Caernarvonshire and Anglesey Paediatric Club
President: Dr. E. Simmons
Secretary: Dr. Margaret Slater
2, Brynteg Terrace,
Bangor, North Wales.

Kent Paediatric and Child Health Society
President: Richard Church, Esq.
Secretary: Dr. E. L. Huppert
12, Montpelier Row,
Blackheath, London, S.E.3.
Chairman: Dr. Gladys Stableforth

The Leeds Regional Paediatric Club
President: Dr. J. G. Jamieson
Secretary: Dr. R. J. Pugh
Department of Child Health,
The Medical School,
Leeds, 1.

Leicester Paediatric Club
President: Dr. J. Vernon Braithwaite
Secretary: Dr. Leo Hahn
71, Knighton Drive,
Leicester.

Manchester Paediatric Club
President: Dr. G. M. Komrower
Secretary: Professor Wilfrid Gaisford
Department of Child Health,
St. Mary's Hospital,
Manchester, 13.

Midland Regional Paediatric Society
President: Dr. Jean M. Mackintosh
Secretaries: Dr. W. H. P. Cant and Dr. B. S. B. Wood
The Children's Hospital,
Ladywood Road,
Edgbaston,
Birmingham, 16.

Sheffield Regional Paediatric Society
President: Dr. A. P. M. Page
Secretary: Dr. R. R. Gordon
58, Nether Edge Road,
Sheffield, 7.

BOOK REVIEWS

Ministry of Education: Publications.

The Ministry of Health is the *fons et origo* of many a pronouncement regarded by paediatricians, but our older patients are also affected by the Ministry of Education. Among its publications which deserve notice are the following:

Memorandum on the Closure of Schools and Exclusion from School on Account of Infectious Illness. (Pp. 20. 1s. 3d.) London: H.M.S.O. 1956. (Issued jointly with the Ministry of Health.)

This memorandum was first issued in 1909, and last in 1942. The new edition brings us up to date in the subject, which is concisely indicated in its title, and does not pretend to be a textbook of communicable diseases.

Education of the Handicapped Pupil, 1945-1955. (Pp. 26. 2s.) London: H.M.S.O. 1956.

This interesting booklet reviews recent work in 'the small but important section concerned with the education of handicapped pupils' which followed the Education Act of 1944. Its anonymous author is evidently conscious of history and of current social progress as a continuum.

The Education of Patients in Hospital. Circular 312 (11th September, 1956), circulated to local education authorities, and as an appendix to Ministry of Health Memorandum 'Education in Hospitals', H.M.(56) 81 which is circulated to Regional Hospital Boards, Hospital Management Committees and Boards of Governors of Teaching Hospitals.

These memoranda summarize the regulations governing the schooling of children in hospital, and go somewhat further. It is encouraging to note that in a hospital school 'even short-stay patients should be admitted to its roll' (actually some hospital schools exist now in general children's hospitals or wards in which most of the children are short-stay patients), and that the need to stagger teachers' holidays or engage extra staff during school holidays is recognized; discouraging to find no mention of nursery school teachers; 'Where there is a number of children under seven it may be an advantage to employ a helper to assist the teacher'.

Feeding in Infancy and Early Childhood. By URSULA JAMES. (Pp. 135; 9 figures. 10s. 6d.) London: Faber and Faber. 1946.

This small volume could be read with profit by mothers as well as nurses, medical students and practitioners. Infant welfare officers will find in it a great deal of helpful information. It strikes the happy mean between the rigid schedules of 25 years ago and the loose demands of the moderns. There is a little irritating repetition and the case reports are made to sound synthetic.

The book is full of common sense, which is the root on which all infant care should be grafted, and it contains a great deal of practical value. Dr. James is to be congratulated and the book deserves success.

Die Pathogenese des Morbus Haemolyticus Neonatorum. By G. MARTIUS. (Pp. 70. DM. 9.60.) Stuttgart: Georg Thieme. 1956.

This monograph reviews the literature of haemolytic disease of the newborn with particular reference to the part played in antigen antibody reaction and exchange by the placenta. The main objective was to determine if blood group substances, apart from those of the red blood cells, played any part in sensitization of the mother. A series of absorption experiments using agglutinating and conglutinating Rhesus antisera is presented in which negative results suggested that the placenta is not a source of blood group substances. Some apparent absorption of antibody with reduction of agglutinating serum titre was ascribed to non-specific absorption by such substances as lecithin and cholesterin. A short discussion of the serological findings together with some histological observations ends inconclusively.

Handbook on Poliomyelitis. By JOSEPH TRUETA, A. B. KINNIER WILSON and MARGARET AGERHOLM. (Pp. vii +139; illustrated. 20s.) Oxford: Blackwell Scientific Publications. 1956.

This is a disappointing book. The production is not up to the usual standard of the publishers and from the first chapter the diagrams are confusing because dark heavy lines are not dark enough, due perhaps to the poor quality of the paper. It contains too much about detailed hospital treatment for the family doctor, and yet, if he looks for up-to-date information about immunization, he will find no discussion of the mass trials of the U.S.A., and the brief mention of quarantine measures is frankly misleading. Is father to stay home from work for three weeks? What exactly is mother to do about the shopping? It looks as if Dr. Agerholm is trying to imply the blessing of the Ministry of Health for her published views. For those called upon to treat poliomyelitis in hospital there is more that is valuable although the repeated reference to infectivity is overdone. The practical contributions of the Oxford school to respiratory difficulties are well described although line drawings of circuits would have been better than indifferent photographs of apparatus. Fig. 18, for example, is too complicated to help at all. The section on early diagnosis is the best part of the book. There is no table of contents.

In the review of *Child Behaviour* by Frances L. Ilg and Louise Bates Ames, in the December, 1956, issue (*Arch. Dis. Childh.*, 31, 534), it was erroneously said that the Gesell Institute of Child Development was at Yale University.

BRAIN DAMAGE AFTER FEBRILE CONVULSIONS

BY

MALCOLM FOWLER

From the Adelaide Children's Hospital, South Australia

(RECEIVED FOR PUBLICATION NOVEMBER 5, 1956)

Despite the suggestions of several writers on the importance of convulsive seizures in infancy as an aetiological factor in the development of cerebral palsies, little attention is given to this association in the standard texts in general medicine and pathology, or even in the more special treatises on diseases of the nervous system. It is not altogether surprising, therefore, that convulsions occurring in the course of febrile illnesses are often not treated with the gravity and urgency they deserve. Because convulsions are so frequent an accompaniment of relatively innocuous infections and in most cases leave the patient apparently normal, the paediatrician may regard both a convulsion of purely febrile origin and the resulting signs of nervous disease as common manifestations of some other intracranial process.

The following five cases are presented in the hope that the potentially lethal nature of convulsions will be more widely acknowledged.

Materials and Methods

The pathological material was obtained from necropsies performed at the Adelaide Children's Hospital during the years 1954 to 1956 inclusive. Before immersion of the intact brain pieces were removed for fixation in formol-ammonium bromide, and in two cases samples were kept for animal inoculation. After prolonged fixation complete coronal slices of the cerebral hemispheres and smaller pieces of brain-stem and cerebellum were embedded in celloidin and paraffin, and stained by Weil's method for myelin sheaths, with Nissl's stain, and by haematoxylin, counterstaining with both eosin and van Gieson's mixture. Frozen sections were used for the metallic impregnation of neurofibrils and astrocytes using Bielschowsky's and Cajal's methods, respectively.

Case Reports

Case 1. The patient, previously a healthy boy of 2 years, developed measles two days before admission. He had not been very sick but had been coughing a lot. On the day of admission he was found in his cot at 7.45 a.m. in a convulsive attack, blue and frothing at the mouth. This continued until 9.30 a.m. when the convulsion was controlled by ether anaesthesia in the Casualty Department of the Adelaide Children's Hospital where his colour was described by the Admitting Officer as ' almost black '.

On examination in the ward his temperature was 103° F., he was slightly cyanosed, with a cold skin on which there was a fading measles rash. The pupils were equal and reacted sluggishly to light. The fundi oculorum were normal. The fauces were moderately reddened, the right tympanic membrane was dull and slightly bulging. Air entry into the lungs was good but there were many rhonchi. The abdomen was normal. Reflexes were absent in the limbs. Slight neck stiffness was present for an hour after the convulsions had ceased.

SPECIAL INVESTIGATIONS. The cerebrospinal fluid was under a pressure of 100 mm. of water, contained 28 mg. protein per 100 ml. and no cells. The white blood count was 24,000 per c.mm., of which 81% were polymorphonuclear leucocytes.

COURSE. In the evening of admission he went pale, with a blood pressure of 70 mm. systolic and 40 mm. diastolic. This collapse was treated by intravenous serum infusion. The next morning he had a further convulsive attack which lasted for 10 minutes. He was comatose from the time of his first convulsion, responding by groaning to painful stimuli, and died three days after admission.

POST-MORTEM FINDINGS. The necropsy (No. 41/56) was performed 22 hours after death. The body was well-nourished and on the skin of the back and face were the remains of a macular rash. In the lungs were numerous haemorrhagic areas of consolidation and these on microscopic examination were confirmed as foci of confluent haemorrhagic bronchopneumonia. *Staphylococcus aureus* was cultured from the lungs. There was severe centrilobular necrosis in the liver, involving about one half the thickness of the lobule. The liver cords were disorganized, and the cells were intensely eosinophilic and shrunken, with pyknotic nuclei. Many cells were disrupted into granular fragments. There was no inflammatory reaction in the portal areas and there was no vascular congestion.

In the spleen there were large reactive centres and reduced numbers of lymphocytes in the Malpighian bodies.

Central Nervous System. No abnormality apart from much congestion was noted in the brain on naked-eye examination. Microscopically, however, there was a widespread necrosis of neurones. The affected cells

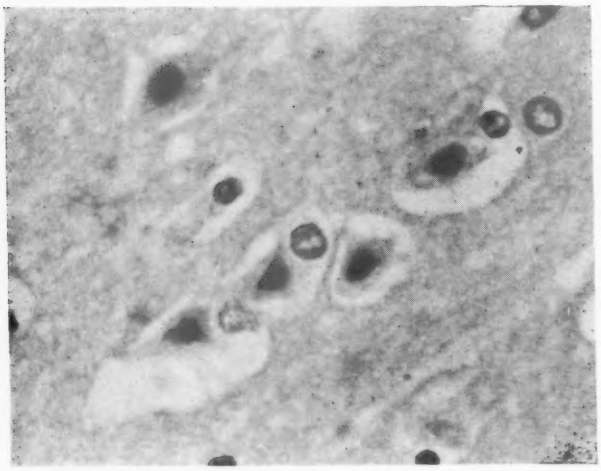

FIG. 1.

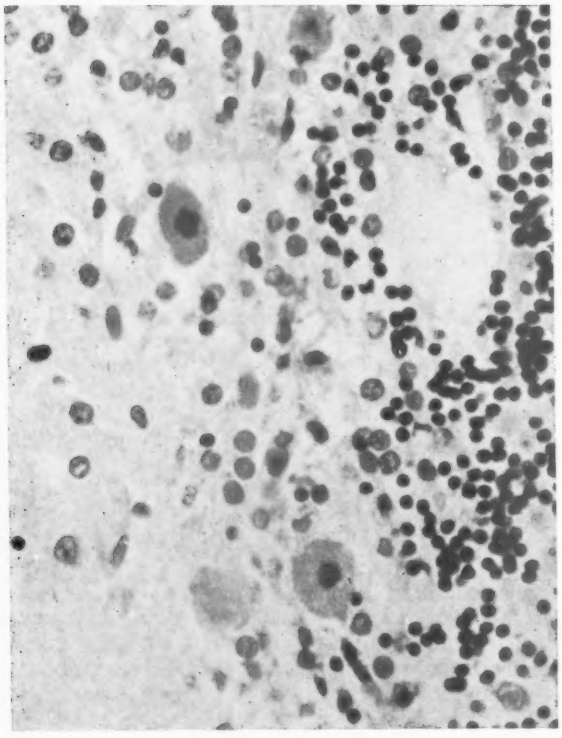

FIG. 2.

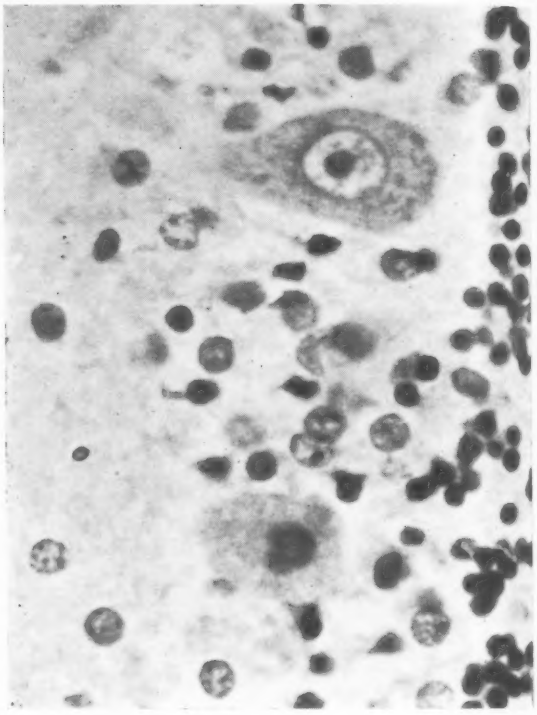

FIG. 3.

FIG. 1.—Case 1: frontal cortex showing shrunken neurones with pyknotic nuclei, and pericellular vacuolation. Haematoxylin and eosin ×700.

FIG. 2.—Case 1: cerebellum showing shrunken Purkinje cells with pyknotic nuclei. Haematoxylin and eosin ×450.

FIG. 3.—Case 1: cerebellum showing a normal and a necrotic Purkinje cell. Haematoxylin and eosin ×825.

were shrunken, their cytoplasm was brightly eosinophilic, all Nissl material having disappeared, and the nucleus was small, irregular in shape and pyknotic (Fig. 1). Often the nucleolus was enlarged and eosinophilic. The blood capillaries in these areas were moderately or greatly dilated, but there was no haemorrhage or softening and only occasionally were a few small round cells seen in the perivascular space. In addition to neuronal damage, the astrocytes in the affected grey matter were also abnormal in that they failed to impregnate with gold although their nuclei did not look abnormal using haematoxylin stains. Astrocytes in the white matter underlying the cortex stained normally but those on the junction were incompletely impregnated and often appeared to have fragmented processes. In most areas there was much perivascular and pericellular vacuolation.

All parts of the cerebral cortex were involved but particularly the temporal and frontal gyri. The occipital cortex, the hippocampus and dentate fascia were damaged on both sides, but far more severely on the left side. The thalamus and amygdaloid nucleus on both sides showed an equally severe degree of neuronal

necrosis, but the lesions in the caudate nucleus were more extensive on the left. The putamen and globus pallidus showed only pericellular oedema on the right but were severely damaged on the left. Small focal lesions were present in the left claustrum. In the cerebellum there was selective damage to the Purkinje cells, other cells of the cortex and the central nuclei being unaffected. On the whole there was not much damage in the cerebellum, but two areas involving several adjacent folia were present, one in the vermis, the other in one lateral lobe. In these foci the majority of the Purkinje cells were shrunken, with brightly eosinophilic cytoplasm and contracted densely staining nuclei (Fig. 2). Many had completely disappeared and others were merely faint outlines. Often a normal Purkinje cell would be found amongst degenerate neighbours (Fig. 3). In other parts of the cerebellar folia the Purkinje cells showed patchy chromatolysis.

Case 2. This child, a boy aged 1 year, was admitted with a two days' history of anorexia, drowsiness and running nose. The night before admission he had had a convulsion unrelieved by intramuscular phenobarbitone but stopped by ether anaesthesia. The attack lasted about half an hour. He had begun convulsing again in the morning at 6.15 o'clock and was still convulsing when first seen in the Casualty Department at 7 a.m. The child was very cyanosed. After treatment with phenobarbitone and ether the convulsions stopped at about 7.15 a.m.

On examination in the ward he was unconscious and pale, with cyanosed lips. His temperature was 104° F. There was some residual intermittent twitching of the right arm and leg. The fundi oculorum were normal and the ear drums slightly reddened. There was no neck stiffness, and the thorax and abdomen were normal. The knee and ankle jerks were absent and the plantar reflexes were flexor.

SPECIAL INVESTIGATIONS. A sample of cerebrospinal fluid, taken immediately after admission, was not under increased pressure, and contained 14 white blood cells, and 1,060 red blood cells per c.mm., 60 mg. protein, and 35 mg. sugar per 100 ml. Further lumbar punctures on the fifth and eleventh days of his illness yielded fluid again contaminated with blood. The blood contained 21,000 white cells per c.mm. of which 80% were polymorphonuclear leucocytes. Radiological examination of the chest showed no sign of disease. Blood culture was negative and no abnormal organisms were found in the faeces. The urine was normal.

COURSE. Two days after admission the features of a right hemiplegia, previously indefinite, emerged clearly, the facial and peripheral musculature on this side being paralysed, with exaggerated tendon reflexes and extensor plantar response. His temperature was consistently at or above 103° F. A few days before death the coma lightened enough for him to be able to respond by groaning to painful stimuli. He died on the twelfth day of illness in a state of dehydration, deeper coma and subnormal temperature.

POST-MORTEM FINDINGS. The necropsy (No. 94/55) was performed 18 hours after death. There was a purulent right otitis media, and confluent bronchopneumonia. Yellow streaks were found in the pectoralis minor muscles. There was necrosis of all papillae in the left kidney, but of only one papilla in the right. All these lesions were confirmed microscopically, the muscle changes being those of necrosis and calcification, probably secondary to rupture during the convulsion. The pulmonary and renal changes were both very recent.

Central Nervous System. The parietal lobes, particularly on the left, were hyperaemic. On section the cortical grey matter of the left cerebral hemisphere was peppered with fine red dots. The dural sinuses were normal.

Microscopically the basic lesion was degeneration of neurones. In the most severely affected areas the nerve cells had disappeared but in other places many were still present and showed degenerative changes—shrinkage, loss of Nissl substance, acidophilia of the cytoplasm, pyknosis and enlargement of the nucleolus which was weakly acidophilic (Fig. 4). Coincident with loss of the nerve cell body was a great scarcity of axonal processes, and many showed beading and fragmentation. In the central white matter of the cerebral hemispheres myelin sheaths were finely beaded. In the affected grey matter microglial proliferation was obvious, sometimes as amoeboid forms, but more conspicuous was the pleomorphic rod-cell stage. Even in areas of cortex where degenerate neurones were still visible normal astrocytes could not be demonstrated by Cajal's gold impregnation method, except in the subpial layer where they were increased. Astrocytes were present in large numbers in the immediately subcortical white matter, and here they were impregnated clearly (Fig. 5). Abnormal forms could be seen in the junction between cortical grey and white matters and in the deeper parts of layer I in the cerebral cortex (Fig. 6). The capillary vessels in the affected grey matter were extremely numerous and their endothelial and adventitial nuclei were very prominent (Fig. 7). There was a very occasional slight infiltration of lymphocytes around larger vessels. The meninges were thickened and contained an excess of macrophages.

The grey matter of the left cerebral hemisphere was very severely affected. The lesions in the cerebral cortex were diffuse and of approximately equal severity in all the frontal and temporal gyri, the anterior and posterior central gyri, the gyrus cinguli, the insula, the uncus and the fusiform gyrus. The hippocampal gyrus had lost layer III of its cortex for a short segment. There was almost complete loss of neurones in the hippocampus, particularly where its cortex enters the concavity of the dentate fascia. The granule layer of the dentate fascia showed much less outfall, exhibiting scattered small foci and segments of partial or complete loss. In the thalamus, putamen, caudate nucleus and amygdaloid nucleus only a few recognizable cells remained. The globus pallidus showed lesions of lesser severity although in one section all cells had been lost from its inner division. A small focal lesion was seen in the anterior perforated substance, and there were moderate numbers of such foci in the claustrum.

On the right side lesions were very much less pronounced. The cortex was normal, apart from damage

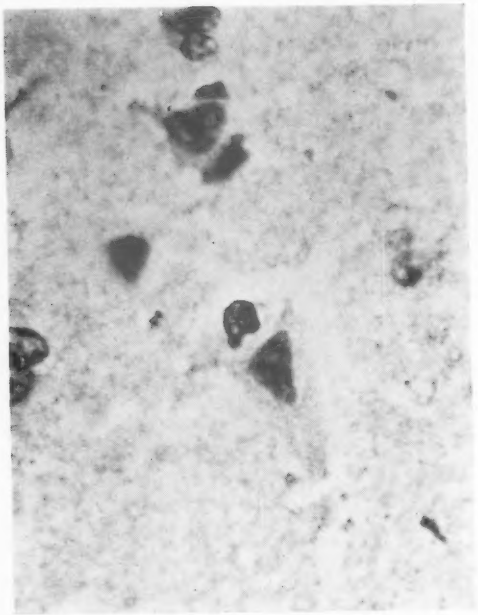

FIG. 4.—Case 2: frontal cortex showing shrunken neurone with pyknotic nucleus, enlarged pale nucleolus and faint cytoplasm.
Haematoxylin and eosin ×790.

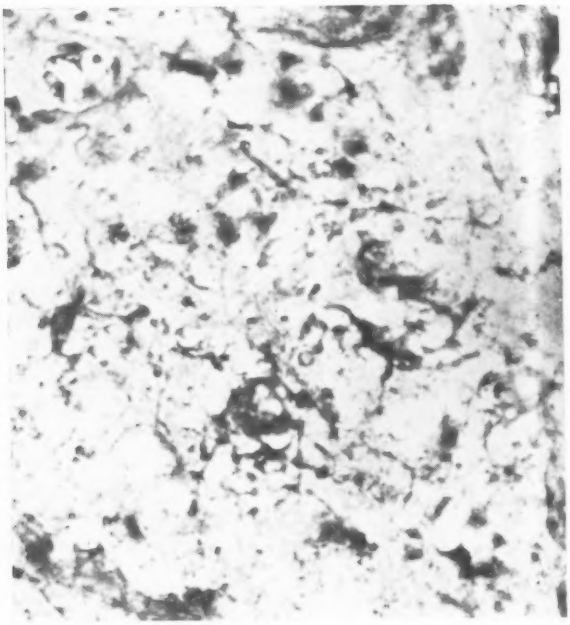

FIG. 6.—Case 2: abnormal astrocytes on the border of grey and white matters of the frontal cortex.
Cajal's gold chloride ×400.

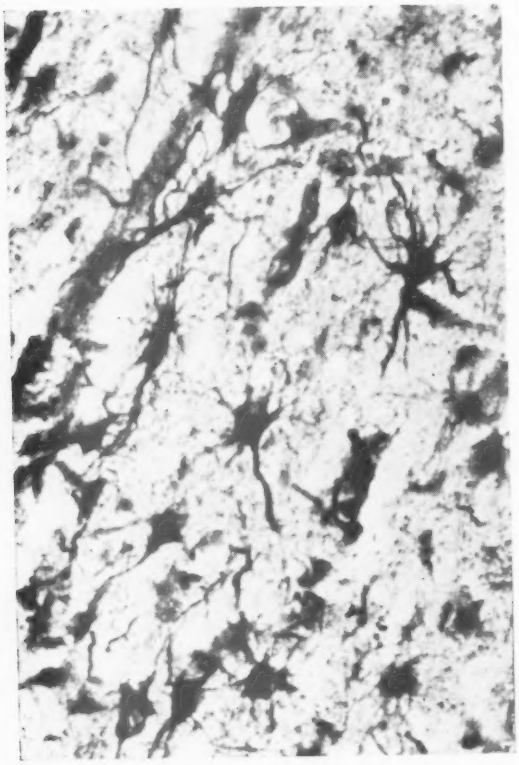

FIG. 5.—Case 2: numerous astrocytes in the white matter immediately beneath the frontal cortex.
Cajal's gold chloride ×400.

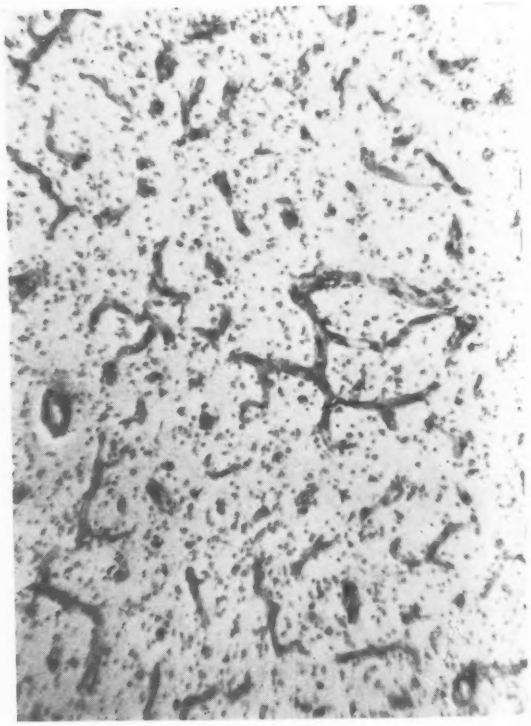

FIG. 7.—Case 2: temporal cortex showing capillary proliferation.
Haematoxylin and eosin ×90.

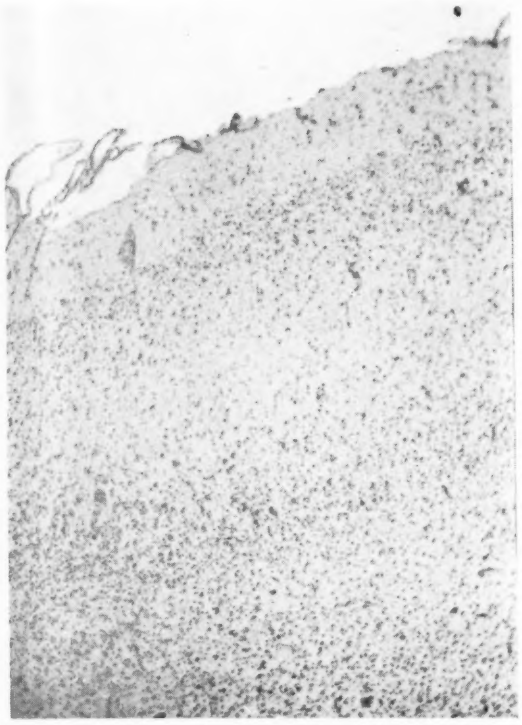

FIG. 8.—Case 2: insular cortex showing loss of neurones in layer III. Haematoxylin and eosin ×30.

to the superior part of the superior temporal gyrus, inferior portion of the insular cortex and to the hippocampal gyrus, and in these portions layer III had been selectively damaged. There was moderate destruction of cells in the anterior nucleus of the thalamus, a small focal lesion in both the hippocampus and the central part of the dentate fascia. The putamen, globus pallidus, caudate nucleus, claustrum and the rest of the thalamus were normal.

Structures of the midbrain, medulla oblongata and cerebellum were normal.

In the cerebral cortex, layers III, V and VI were most severely damaged, and, as stated above, the neurones of layer III were sometimes involved alone (Fig. 8). Layer II often was visible when all deeper layers were completely disorganized.

Case 3. This girl, aged 21 months, had been irritable, feverish and anorexic for a week before admission. On the day before admission she had vomited once and retched several times. At 4.45 p.m. on the day of admission her mother had found her in a convulsive seizure involving all limbs; her skin was blue, cold and sweaty. The fit lasted an hour and was then followed by unconsciousness in which the child's respirations were slow and grunting.

On examination in the ward she was in unrousable coma and breathing irregularly. Her temperature was 102·2° F. and her pulse 160. The eyes were deviated to the left and there was a fine nystagmus to the left. The pupils were moderately dilated, equal and reacted to light. The fundi oculorum were normal. The thorax and abdomen were normal. The legs were hypertonic, without tendon reflexes but with extensor plantar responses. The arms were flaccid, with active reflexes equal on both sides. There was a fine erythematous rash on the trunk and limbs. Four hours after admission she began to convulse and this fit lasted two hours.

SPECIAL INVESTIGATIONS. The cerebrospinal fluid was under a pressure of 260 mm. of water, and contained 4 white cells per c.mm. and 22 mg. protein per 100 ml. The urine contained many granular casts. The white cells in the blood numbered 20,000 per c.mm., of which 62% were polymorphonuclear leucocytes. Neither lead, antimony, arsenic nor mercury was present in the gastric contents. The urine and blood showed no evidence of lead in abnormal amounts. Radiological examination of the skull and chest showed no abnormality. Blood culture was not done.

COURSE. She remained deeply comatose and her limbs became more spastic, the legs in extension, and she gradually developed opisthotonos. After two days at 102° F. her temperature fell to below 100° F. Two further examinations of the cerebrospinal fluid showed normal pressure and no increase in protein; 7 cells per c.mm. were present on one occasion, none on the other. The urine a week after admission was normal. No organisms of a pathogenic nature were isolated from the faeces. She died four weeks after admission in a state of decerebrate rigidity.

POST-MORTEM FINDINGS. The necropsy (No. 13/56) was performed five hours after death. Apart from an early but widespread bronchopneumonia, confirmed microscopically, there were no significant changes except in the brain.

Central Nervous System. There was a slight increase in the space between the cerebral hemispheres and the skull. The frontal lobes were very pale and their convolutions slightly angular. The parietal and temporal lobes were very spongy to touch, and the grey matter of the temporal lobes (even after fixation) tended to fall away spontaneously under the most gentle handling, and was very granular in appearance, with the consistency of stiff porridge. The occipital lobes were firm and vascular by comparison. The central white matter concontained conspicuous capillaries but otherwise was normal. The cerebellum, brain-stem and dural sinuses were normal.

Microscopical examination revealed loss of neurones of variable degree throughout the cerebral cortex and basal nuclei.

In the most severely damaged areas of cortex all neurones had disappeared, resulting in a complete loss of stratification, and the grey matter tended to be fragmented, even in the celloidin sections (Fig. 9). In many areas the thickness of the cortex was already reduced and early tenting of the surface was recognizable. There was much astrocytic proliferation in the white matter immediately beneath the affected cortex, but the astrocytes in the grey matter, apart from those of the subpial

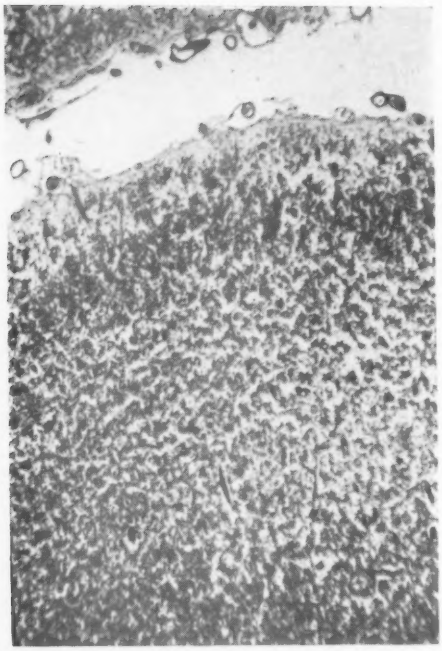

FIG. 9.—Case 3: temporal cortex showing fragmentation. Weil stain ×25.

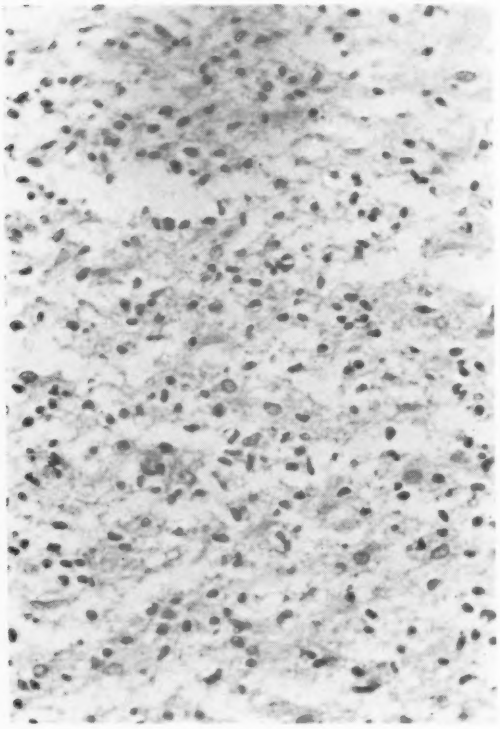

FIG. 10.—Case 3: caudate nucleus showing loss of neurones and microglial proliferation. Haematoxylin and eosin ×250.

layer, were fragmented and impregnated poorly. Axis cylinders were grossly reduced in number, a mere scattering of faintly impregnated fragments remaining. Many areas had suffered minimal loss, perhaps of only one cortical layer, and in this case astrocytic proliferation within the grey matter was marked. Microglia, mostly in the rod-cell stage, were often present in large numbers, except in areas of most severe damage (Fig. 10). Between these extremes all grades of neuronal loss were encountered. A few small strips of cortex were completely normal but the vastly greater part showed some lesions. Capillaries were slightly increased in damaged areas but there was no perivascular or meningeal infiltration by inflammatory cells.

Of the cortex, that in both temporal lobes suffered most severely, all neurones having been lost from all the gyri in the anterior portions of these lobes. Small segments of complete loss were scattered throughout other areas of cortex. All frontal gyri on both sides were severely affected, and lesions were also found in the anterior and posterior central gyri, the cingulate gyrus, insular cortex, the hippocampal gyri and the orbital gyri. A small area, about 1 cm. long, of moderately severe cell loss was present in the cortex of the hippocampus and some lesser damage in the concavity of the dentate fascia. Layers II and IV were the most often preserved, and sometimes for long stretches all other layers had disappeared while these remained. Layers V and VI were on the whole the most severely and frequently involved.

The lateral and anterior parts of the thalamus were considerably damaged, particularly the anterior nucleus, and on one side the amygdaloid nucleus had lost nearly all its cells. The head of the caudate nucleus had suffered much loss on one side whereas only its mid-portion on the other contained lesions and these were very slight. The claustrum on one side showed a few focal areas of loss. The putamen, globus pallidus, substantia nigra, red nucleus and subthalamic nucleus on both sides were normal, nor were any changes found in the cerebellum or medulla. The choroid plexus, meninges and white matter were normal.

Case 4. Until the present illness at the age of 13 months, this patient had developed normally and was alert, intelligent and affectionate. One week before her illness she had not been herself, being restless and irritable after having a haemangioma on the temple treated with carbon dioxide snow. On the day before the convulsion she was hot and drowsy. The next day she had a temperature of 103° F. in the morning but ate a good lunch and had a normal motion. Apart from being hot and having a foul breath she was normal at 3 o'clock in the afternoon. At 4 o'clock she gave a cry and went into a convulsion which lasted two and a half hours, during which her colour was bluish-grey. The doctor took her temperature just after 4 p.m. and found it to be 105° F. She remained unconscious, with intermittent clonic movements all night but her colour was normal. The next morning she passed foul fluid motions full of blood and mucus. She was admitted unconscious to a private

ward. The sample of cerebrospinal fluid taken just after admission was normal. Six weeks later when she was transferred to a public ward, spasticity in flexion of both arms and slight spasticity of the right leg were present, and she lay in bed showing no awareness of her surroundings.

Ten days after admission her temperature rose to 105° F. and the left tympanic membrane bulged a little. This settled down with penicillin treatment but there was intermittent pyrexia over the next month, occasional crepitations being heard in the lungs. Six weeks after admission she had a typical attack of measles and three days after the rash had faded her temperature rose again, as a result of a right otitis media, both drums at this stage being opened under anaesthesia. From the pus obtained pneumococci were cultured. Her temperature fell temporarily, only to rise with the appearance of widespread crepitations in the lungs. Her general condition deteriorated and death occurred 18 weeks after the onset of her illness. She had remained unconscious throughout.

SPECIAL INVESTIGATIONS. Apart from examinations of the cerebrospinal fluid at the beginning of her illness two further samples, both normal, were taken at three weeks and 11 weeks after the onset.

The Mantoux reaction was negative. Blood examination showed little significant abnormality, except for a raised white blood count (21,000 per c.mm.) on one occasion. Sera collected four weeks and 10 weeks from the onset of the illness gave negative complement-fixation reactions against mumps, lymphocytic choriomeningitis and Murray Valley encephalitis viruses.

FIG. 11.—Case 4: atrophy of convolutions of frontal and anterior parietal lobes.

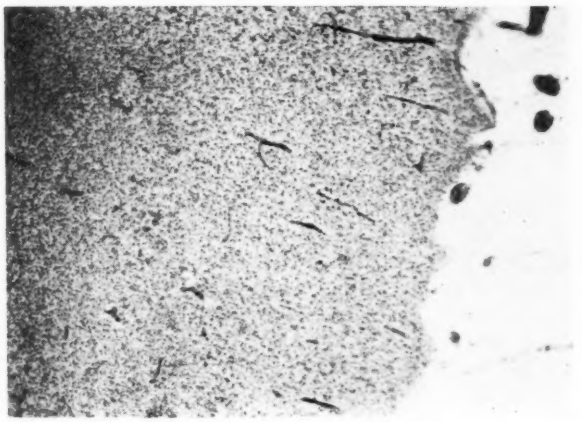

FIG. 12.—Case 4: frontal cortex showing loss of architecture and surface irregularity.
Haematoxylin and van Gieson ×25.

POST-MORTEM FINDINGS. The necropsy (No. 32/54) was performed two hours after death. Apart from general wasting of the body there was a bilateral purulent otitis media and mastoiditis, and terminal bronchopneumonia.

Central Nervous System. Both frontal lobes and the post-central gyri were shrunken with a corresponding increase in cerebrospinal fluid over them. The gyri were narrow and angular and were separated by wide sulci (Fig. 11). The temporal and occipital lobes and cerebellum looked normal. Coronal slicing of the brain in the affected areas revealed irregularity and reduction in thickness of the cortical grey matter and mild reduction in bulk of the central white matter. The basal ganglia were normal.

Microscopic examination showed a mild cellular thickening and increase of collagen fibres in the arachnoid membrane, but no inflammatory cells. Neurones had disappeared in greater or less degree throughout the cortex of the gyrus cinguli, the frontal gyri, anterior central and posterior central gyri. The mid-portion of the caudate nucleus, the lentiform nucleus, the hippocampus, amygdaloid nucleus, mammillary bodies, lateral part of the thalamus, brain-stem and cerebellum, and the temporal gyri were normal. The head of the caudate nucleus, midbrain, occipital cortex and other parts of the parietal cortex and thalamus were not examined microscopically. Large parts of the cortex were extremely thin, with almost complete loss of neurones and with surface tenting (Fig. 12). In areas of lesser severity the layering of neurones was severely disturbed, layers III and V apparently suffering most. Even when other layers had completely disappeared layer II was often still recognizable. No Betz cells were seen. Coincident with the disappearance of neurones was an extreme reduction in nerve fibres, and an increase in astrocytes, particularly in layers V and VI and in the adjacent white matter. In the white matter there was a diffuse pallor together with vacuolation of remaining

myelin sheaths and there were numerous grape-like bodies. Capillaries had increased slightly in number, but were not accompanied by any infiltration of inflammatory cells in their adventitial zones.

Case 5. This girl was first admitted at the age of 10 months for treatment of scurvy, having had no vitamin additions to her diet of cows' milk and 'farex'. After treatment with ascorbic acid and iron for a fortnight the child was discharged much improved. The following day, however, she was readmitted at 1 p.m. having been convulsing since 7 a.m. On examination she was convulsing and had a temperature of 105° F. The convulsions involved the left side more than the right. The fundi oculorum and pupils were normal. There was no neck stiffness nor any abnormality noted in the chest, abdomen or limbs. Following treatment she came out of the convulsive state but was comatose, responding to painful stimuli by withdrawal, and the limbs were spastic.

SPECIAL INVESTIGATIONS. The haemoglobin value was 8 g. % and the white blood cells numbered 28,000 per c.mm., 92% being polymorphonuclear leucocytes. The urine contained numerous granular casts. The cerebrospinal fluid, which was not under increased pressure, contained 21 mg. of protein per 100 ml., and no cells. Culture of the faeces yielded a *Salmonella* group C organism. Blood culture was negative. The Wassermann reaction was negative. Blood taken five weeks after the illness began had no complement-fixing activity against mumps and Murray Valley encephalitis viruses.

COURSE. Her temperature remained elevated until a week after admission when it returned to normal, and at this time a further culture of the faeces was negative for *Salmonella* organisms. The child's state of consciousness, however, improved very little. She lay in bed unaware of her surroundings, often breaking into spasms of high-pitched crying. She remained spastic in all limbs, the arms being held in flexion. Her eyes showed conjugate deviation to the right, and there was intermittent coarse nystagmus. The pupils reacted to light and were equal but she showed no awareness of moving objects and she did not respond to auditory stimuli. Further examinations of the cerebrospinal fluid yielded normal results. She was finally discharged two and a half months after the onset of her illness—spastic and comatose, responding only to painful stimuli, and still prone to outbursts of prolonged crying.

Virus Examination

Apart from complement-fixation tests on sera from Cases 4 and 5 during life, pieces of frontal cortex, basal ganglia, cerebellum and medulla selected from Cases 2 and 3 were submitted to the Institute of Medical and Veterinary Science, Adelaide, for virus isolation. The material was inoculated into newborn and weaned mice, on to the rabbit's cornea, into embryonated eggs and HeLa cell tissue culture. No viruses were recovered.

Discussion

Scholz (1951) has published his findings in the brains of children dying after severe febrile convulsions, but his monograph is not available to the present writer. However, Meyer, Beck and Shepherd (1955) refer to his work in their paper describing the cerebral lesions in a boy of 9 years who suffered from status epilepticus a year before death. They found neuronal damage in various parts of the cerebral cortex, in the basal ganglia and cerebellar cortex. They accepted Scholz's view that brain lesions may be directly due to a convulsive disorder. Before considering the part played by the convulsions in the present cases it is first necessary to exclude the action of other well-recognized causes of cerebral disease.

In this series of cases, all the children were mentally and physically normal before the onset of the illness, except for Case 5 who has scurvy. The oldest child was 2 years. The precipitating illness was gastro-enteritis in two cases, upper respiratory infection in one, measles bronchopneumonia in one and undiagnosed in one. In all cases the temperature at the onset was above 102° F. and in two cases reached 105° F. The length of the convulsions was not easy to determine for two patients were already in the attack when found, but the shortest time was one hour (Case 3) and the longest time at least six hours. None of the patients recovered consciousness and as the residual twitchings faded various degrees of spastic paralysis appeared—complete quadriplegia in three cases, diplegia and hemiplegia each in one case.

The usual clinical diagnosis of encephalitis made in these cases was not confirmed by lumbar puncture, for the cerebrospinal fluid, apart from raised pressure in one instance, was normal. In Case 2 only bloody taps were obtained.

One of the children is still alive but pathological examination of the other four cases revealed damage to various parts of the cortex and basal ganglia. In Case 4 the frontal lobes and post-central gyri were involved bilaterally, all other areas examined being normal. The temporal and frontal lobes were severely damaged bilaterally in Cases 1 and 3, unilaterally in Case 2, but in this last case the superior temporal gyrus was selectively involved on the other side. Layer III was the most frequent and often only cortical layer showing disease, layers V and VI being involved next in frequency. The thalamus, caudate and amygdaloid nuclei were damaged in three cases, often severely, but in Case 2 unilaterally. The hippocampus contained lesions in three cases, severe in Cases 1 and 2. Lesions in the claustrum tended to be focal and small, unlike the diffuse

lesions in the other nuclei. Damage of moderate severity was found in the lentiform nucleus in two cases. Only in Case 1 did the cerebellum show lesions, which consisted of small scattered groups of necrotic Purkinje cells. No lesions were found in the midbrain, pons or medulla. The choroid plexuses, cerebral arteries and dural sinuses were normal. There was no evidence of inflammatory reaction around the blood vessels or in the meninges, nor did the vessels contain thrombi or other significant abnormality, although in some cases they were somewhat dilated and in Case 2 greatly increased in number. No signs of perivascular demyelination or inflammation were found in the white matter and these were deliberately sought in the patient who had suffered from measles. The first four cases illustrate a progress of the changes from necrosis to disappearance of nerve cells, followed by astrocytic and microglial proliferation. An interesting finding in the three cases of shorter duration was the inability to impregnate astrocytes in areas of neuronal damage, associated with abnormal astrocytic forms in the border zones. In Case 4, however, of 18 weeks' duration, astrocytic proliferation was easy to demonstrate.

In Cases 2 and 3 tissue culture and animal inoculation failed to provide evidence for the presence of viruses in brain tissue removed at necropsy, and serum from Cases 4 and 5 gave negative complement-fixation reactions. Case 5 is included, in spite of the lack of pathological proof, for the clinical findings are very similar to the other cases, and she is in a state of mental defectiveness and blindness most compatible with widespread cortical damage. An alternative diagnosis of haemorrhage due to scurvy is unacceptable for several reasons, the main ones being that there was no evidence of haemorrhage elsewhere and that the child had responded well to treatment. Moreover, haemorrhage great enough to damage the occipital and frontal cortex is most unlikely without signs of increased pressure or other abnormalities in the cerebrospinal fluid.

It seems clear, therefore, that these children were suffering from febrile convulsions, of a prolonged, severe type, and that brain damage occurred during the convulsion. The five cases appeared during a two-year period in a 300-bed hospital so that the condition cannot be called rare. In contrast, Cary (1956), in a series of 100 cases of infantile febrile convulsions, found little evidence of serious cerebral impairment. This failure may well be due to exclusion of some grave cases on the grounds that they represent the convulsive prelude to encephalitis or other primarily cerebral disease. It is probable that some of the cases of mental deterioration after convulsions reported by Illingworth (1955) are examples of the same process described here. In my Case 4 a little less damage to the frontal lobes without involvement of the motor area could have led to mental changes alone.

The pathogenesis of the neuronal necrosis is not certain. Toxaemia from the infection is unlikely, for changes in the brain of the type and severity under discussion are not a feature in children dying of much more severe and prolonged infections. Direct action of microorganisms is a theory not supported by any of the findings. The two most acceptable theories are that either the nerve cells degenerate from the effects of the general anoxia which occurs during a convulsion or that there is a specific mechanism in the brain producing local anoxia. The unilateral character of the degeneration in Case 2 may be interpreted in favour of a local mechanism, although it is probable that individual cellular or lobar metabolic activity in the brain may influence the degree of susceptibility to general anoxia, e.g., the Purkinje cells illustrated in Fig. 3. This regional character of lesions resulting from what might reasonably be thought of as a generally acting disease process has been mentioned by Southcott and Fowler (1954) in relation to acute haemorrhagic leucoencephalitis. Against the participation of local vascular spasm in the causation of the changes is the conclusion of Penfield and Jasper (1954) that during an epileptic seizure the cortex, contrary to general opinion, does not blanche and that its blood flow is actually increased. In Case 1 the changes in the liver are very suggestive of anoxic degeneration, particularly in view of their central localization in the lobule, without inflammatory reaction. The lesions in the liver may. however, have been an effect of toxaemia, although I have never seen this phenomenon in other cases of equally severe and widespread bronchopneumonia due to *Staphylococcus aureus*. Anoxia as an important factor in centrilobular necrosis of the rabbit liver, particularly in conjunction with low blood pressure, has been shown by McMichael (1937) who concluded that due to the low oxygen tension in its mixed arterial and venous supply the liver is especially liable to suffer in states of general anoxia.

Several authors have reported the association of infantile infections with cerebral disease similar to the cases described here, but they have interpreted the association very differently. Woolf (1955) described the brain changes in three patients dying five, eight and 16 years after the sudden onset of a convulsive illness associated with infection. He thought the cerebral changes were due to dural

sinus thrombosis, but, owing to the nature of his material, he did not have the opportunity to demonstrate the presence of old thrombi. Hallman, Hjelt and Tähka (1956) report the findings in two infants with gastro-enteritis. Both of their patients had convulsions early in the illness. These authors attribute the brain lesions to dehydration and the resulting vascular stasis. Kramer's clinical account (1954) of gastro-intestinal disturbance and cerebral damage includes four cases beginning acutely with convulsions.

A unique case is that of Crome (1952). Encephalopathy in the later stages of gastro-enteritis occurred in the absence of a history of convulsions. Crome attributed the cerebral changes to anoxia following dehydration and vascular stasis. The rarity of such an association is most unusual considering the extreme degrees of dehydration commonly produced by gastro-enteritis in infants. Nevertheless, the present cases demonstrate that similar lesions can occur in the absence of both gastro-enteritis and dehydration. The commonest factor found in all the reported examples, apart from Crome's case, is the presence of convulsions.

Putting aside the question of pathogenesis, several further aspects of the process are of importance. Meyer, Beck and Shepherd (1955) have interpreted the degeneration in the thalamus of their case as a retrograde effect, and therefore likely to throw light on the cortico-thalamic connexions. In Cases 1 and 2 the nerve cells of the thalamus and cortex were at the same stage of degeneration suggesting rather that the damage was simultaneous and not consecutive. Quite apart from this consideration these writers emphasize the importance of the lesions as foci for convulsive seizures in those patients who survive, particularly in reference to temporal lobe epilepsy. In their case and in three of the present cases the temporal lobes suffered severely. It is likely, moreover, that damage following febrile convulsions in early infancy may be the basis for many of the spastic conditions, such as Little's disease, infantile hemiplegia and other variants, with or without dementia, and of behaviour disorders.

Summary

Five children, aged up to 2 years, and previously normal except for one with scurvy, suffered from a prolonged convulsion at the beginning of febrile illnesses comprising gastro-enteritis (two cases), measles bronchopneumonia (one case), upper respiratory tract infection (one case) and unidentified (one case).

The patients remained unconscious after the convulsions, which lasted from one to six hours, but developed various spastic paralyses, and in four cases death occurred four days, 12 days, four weeks, and 18 weeks from the onset of the convulsion. Pathological examination revealed neuronal necrosis of variable distribution and severity in the cerebral cortex, basal ganglia and cerebellum, with no evidence of the direct action of microorganisms. The changes are considered to be the result of systemic anoxia of convulsive origin or, less likely, to be due to a specific mechanism acting locally in the brain. Alternative explanations put forward by other observers are discussed, and it is conceded that stagnation anoxia following dehydration in gastro-enteritis may be responsible on rare occasions. The importance of convulsive cerebral degeneration as a precursor of epilepsy and as the cause of infantile spastic and behaviour disorders is mentioned.

My thanks are due to the various members of the honorary medical staff who have kindly allowed me to use their case notes, and to the Board of Management of the Adelaide Children's Hospital for permission to publish these investigations. The virus examinations were kindly undertaken by Dr. Peter Warner and Dr. Alan Duxbury, of the Medical Research Division of the Institute of Medical and Veterinary Science, Adelaide.

References

Cary, W. (1956). *Med. J. Aust.*, **2**, 254.
Crome, L. (1952). *Archives of Disease in Childhood*, **27**, 468.
Hallman, N., Hjelt, L. and Tähka, H. (1956). *Ann. paediat. Fenn.*, **2**, 31.
Illingworth, R. S. (1955). *Archives of Disease in Childhood*, **30**, 529.
Kramer, W. (1954). *Ned. T. Geneesk.*, **98**, 3631. Quoted by The Year Book of Neurology, Psychiatry and Neurosurgery, 1955-56 Series, p. 167.
McMichael, J. (1937). *Quart. J. exp. Physiol.*, **27**, 73.
Meyer, A., Beck, E. and Shepherd, M. (1955). *J. Neurol. Neurosurg. Psychiat.*, **18**, 24.
Penfield, W. and Jasper, H. (1954). *Epilepsy and the Functional Anatomy of the Human Brain*. Boston.
Scholz, W. (1951). *Die Krampfschädigungen des Gehirns*. Berlin. Quoted by Meyer, Beck and Shepherd, above.
Southcott, R. V. and Fowler, M. (1954). *Med. J. Aust.*, 2, 65.
Woolf, A. L. (1955). *J. ment. Sci.*, **101**, 610.

SOME INVESTIGATIONS ON THE METABOLISM OF PHENYLALANINE AND TYROSINE IN CHILDREN WITH VITAMIN C DEFICIENCY

BY

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Scorbutic children excrete some amino-acids in amounts higher than normal in their urine (Jonxis and Huisman, 1954). Serine, threonine, glycine, histidine, lysine, β-amino-isobutyric acid, glutamic acid in bound form and also tyrosine are excreted in increased amounts. It has been known for a number of years that vitamin C is necessary for the normal metabolism of tyrosine. Levine, Gordon and Marples (1941) found that a number of intermediates in the metabolism of tyrosine appeared in the urine of premature infants when these infants received a diet high in protein and without vitamin C. The same was found when relatively large amounts of tyrosine or phenylalanine had been added to the food. When vitamin C was given the excretion of the tyrosyl substances decreased. Sealock and Silberstein (1940) found that giving high doses of tyrosine to scorbutic guinea-pigs increased the excretion of homogentisic acid, para-hydroxy-phenylpyruvic acid and para-hydroxy-phenyl-lactic acid.

When L-tyrosine is given to scorbutic infants (Morris, Harpur and Goldbloom, 1950; Woodruff, 1950), to human adults (Rogers and Gardner, 1949) or to scorbutic monkeys (Salmon and May, 1950, 1953) the excretion of tyrosyl substances in the urine is increased. After administration of vitamin C the excretion of these tyrosyl substances diminishes. In order to learn more about the tyrosine metabolism in children with scurvy, we have studied the influence of oral doses of phenylalanine and tyrosine on the plasma levels and the excretion of these and other amino-acids in three scorbutic children and one normal child.

Case Notes

The first child, a boy of 17 months, with a body weight of 8·4 kg., was admitted to hospital because he had painful legs. At home he had been mainly fed on pasteurized milk which was subsequently boiled. He had had some vegetables, but these were mostly cooked twice. It is very doubtful whether he ever ate any fruit, but he had received vitamin D regularly. There were no signs of rickets; the serum calcium level was 10·8 mg. per 100 ml., the inorganic phosphorus 5·4 mg. per 100 ml., alkaline phosphatase 14·4 King-Armstrong units per 100 ml. A radiograph of the knees and wrists showed fully developed scurvy. There were periosteal haemorrhages of the femora, but he had no haemorrhages in the skin or gums. The concentration of vitamin C in the blood was less than 0·1 mg. per 100 ml.

In hospital the child was given a diet with 1·2 g. of protein per kg. body weight. A 24-hour specimen of urine was collected. The next day he received in addition to food 1 g. of DL-phenylalanine each hour orally over a period of 10 hours (L-phenylalanine was not available to us). The urine was collected during this period and the next 10 hours. Some days later the same experiment was repeated, but instead of DL-phenylalanine, L-tyrosine in the same amount was given. Thereafter he was given 100 mg. vitamin C daily. With this treatment he soon recovered and the radiological signs of scurvy quickly disappeared. It was not possible to get enough blood from this child to determine the plasma amino-acid composition.

The second child was a boy of 7 months with a body weight of 7·8 kg. He was admitted to the hospital with the diagnosis of tetany. His only food had been boiled pasteurized cow's milk with sugar; neither vitamin C nor vitamin D had been given. On admission the concentration of vitamin C in the blood was 0·3 mg. per 100 ml., serum calcium 7·5 mg. per 100 ml., inorganic phosphorus 4·4 mg. per 100 ml. and alkaline phosphatase 61 King-Armstrong units per 100 ml. A radiograph showed signs of rickets and perhaps of scurvy. The child was given 300,000 i.u. vitamin D_2 and was fed with boiled pasteurized milk without the addition of vitamin C for the next 14 days. At the end of this period the serum calcium level was 10·5 mg., inorganic phosphorus 7·6 mg. per 100 ml. and a radiograph showed that the rickets were healing. The vitamin C concentration in the blood was now 0·2 per 100 ml. In the next few days he was given 10 g. of DL-phenylalanine as described above for the previous child. Five hours after the first dose of phenylalanine a blood specimen was taken to determine

the plasma levels of the various amino-acids. In this case we were not able to collect the 20-hour urine specimen during the phenylalanine administration.

The third child, an 8-month-old girl with a body weight of 7·4 kg., had been sent to the hospital with a diagnosis of tetany. She also had been fed on pasteurized milk with sugar, and had received no greens or fruit. A radiograph showed moderate rickets and scurvy. The vitamin C concentration in the blood was less than 0·2 mg. per 100 ml., serum calcium 5·9, inorganic phosphorus 6 mg. per 100 ml., alkaline phosphatase 61 King-Armstrong units per 100 ml. The child was given 300,000 i.u. vitamin D_2 orally and calcium gluconate intravenously, but no vitamin C was added to the food. After a fortnight a radiograph showed healing of the rickets. The blood levels for phosphate and calcium were about normal at that time: serum calcium 9·8 mg. per 100 ml., phosphate 5·5 mg. per 100 ml.; alkaline phosphatase was still high, 66·6 King-Armstrong units. The vitamin C concentration in the blood remained low during this period and 14 days after admission was 0·2 mg. per 100 ml. Then 10 g. L-tyrosine were given in oral doses of 1 g. each hour; five hours after the first dose blood was withdrawn for the determination of the different amino-acids.

A normal boy, 14 months old, body weight 8·4 kg., who received a diet with 1·4 g. protein per kg. body weight, served as a control. This child had been given 800 i.u. of vitamin D_2 and 50 mg. vitamin C daily for the previous weeks. He was given 10 g. of DL-phenylalanine and 10 g. of L-tyrosine with an interval of about one week. Both times blood was withdrawn five hours after the first doses, and a 20-hour specimen was collected.

Methods

The total amino-acid concentrations in blood and urine were determined using the Van Slyke ninhydrin method (Van Slyke, Dillon, MacFadyen and Hamilton, 1941). The separate amino-acids were estimated with ion-exchange chromatography. A slightly modified gradient elution technique of Stein and Moore was used (Stein, Bearn and Moore, 1954; Moore and Stein, 1954). The concentration of the different amino-acids in the plasma was determined by the same method. In this case a protein-free ultrafiltrate of the plasma was used as has been described previously (Huisman, 1954). For the determination of the tyrosyl substances the method of Medes (1932) was used. The total concentration of keto-acids was measured by the technique described by Felix and his co-workers (Felix, Leonhardi and Glasenapp, 1951; Felix and Schaefer, 1950). For the determination of the homogentisic acid the iodometric titration method of Neuberger (1947) was used.

Results

Table 1 gives the values for the excretion of alpha-amino nitrogen before and after hydrolysis in the urine of the first patient and of the control before and after the phenylalanine and tyrosine loads. As has been described previously (Jonxis and Huisman, 1954), the alpha-amino excretion of the scorbutic child was higher than normal before any additional amino-acid was given. The administration of 10 g. of DL-phenylalanine produced approximately equal rises in the excretion of alpha-amino nitrogen in the patient and in the control. This might have been expected as DL-phenylalanine is known to be excreted rather easily by a normal person. L-tyrosine produced a moderate rise in excretion of free α-amino nitrogen in the scorbutic infant. In the control child the excretion hardly changed. It is noteworthy that the total nitrogen excretion did not increase significantly on the days that phenylalanine or tyrosine had been given. This may be explained by the smaller food intake during these days.

Table 2 shows the excretion of the individual amino-acids during the DL-phenylalanine and L-tyrosine administration in Case 1 and the control, and Table 3 the amino-acid composition of the plasma ultrafiltrates of Cases 2 and 3 and of normal control children. For technical reasons it was not possible to determine the excretion in the urine and the plasma levels of the different amino-acids of the patients and the controls before the administration of DL-phenylalanine and L-tyrosine. We have,

TABLE 1

EXCRETION OF TOTAL AND α-AMINO NITROGEN BEFORE AND DURING ADMINISTRATION OF DL-PHENYLALANINE AND L-TYROSINE IN SCURVY

Patient	Treatment	Urine Volume (ml./20 hr.)	Total Urine Nitrogen (mg./20 hr.)	Urine α-Amino Nitrogen (mg./20 hr.)	
				Before Hydrolysis	After Hydrolysis
Scorbutic Case 1	—	220	2,950	52·5	84·0
	DL-phenylalanine load*	305	2,570	166·5	205·0
	L-tyrosine load*	170	2,420	66·5	104·0
Control	—	320	2,550	32·5	63·0
	DL-phenylalanine load*	410	2,940	156·0	248·0
	L-tyrosine load*	300	3,270	36·0	74·0

* 10 g. of each amino-acid given by mouth.

TABLE 2

URINARY EXCRETION OF FREE AMINO-ACIDS* BY SCORBUTIC AND NORMAL CHILDREN BEFORE AND DURING ADMINISTRATION OF DL-PHENYLALANINE AND L-TYROSINE

Amino-acid	Scorbutic Infants			Controls		
	Mean of Two Patients (1)†	Phenylalanine Load Case 1	Tyrosine Load Case 1	Mean of Two Controls (1)†	Phenylalanine Load	Tyrosine Load
Taurine	30·0	6·0	9·5	7·0	3·5	3·0
Aspartic acid	3·0	0·5	4·0	3·5	1·0	1·0
Threonine		14·0	10·5	4·0	6·6	12·0
Serine	64·5	37·0	31·5	11·0	22·5	17·5
Glutamic acid	2·5	2·0	1·0	4·0	5·5	4·0
Proline	2·0	0	0	1·5	0	0
Glycine		44·0	43·5		34·0	35·0
Alanine	96·5	13·0	18·5	16·5	22·5	21·5
Cystine	4·5	4·5	7·0	3·5	4·5	6·0
Valine	8·0	9·0	11·0	1·5	6·0	8·0
Methionine	3·0	3·0	4·5	2·5	2·0	2·5
Isoleucine	3·5	1·0	1·5	2·5	1·5	1·5
Leucine	3·0	2·5	3·0	4·5	—	2·5
Tyrosine	26·5	56·5	251·0	8·5	9·5	51·0
Phenylalanine	6·0	2,235·0	25·0	2·5	1,850·0	8·0
β-alanine complex	19·5	—	—	1·5	—	—
Tryptophane	4·0	—	—	7·5	—	—
Histidine	56·0	44·5	54·5	17·5	37·5	28·0
Lysine	42·0	26·5	17·5	2·5	3·0	4·0
Arginine	1·5	—	—	3·0	—	—

* The values are given in mg./20 hours.
† Multiplied by 20/24.

therefore, compared the figures for plasma concentration and urinary excretion with the average values found for other scorbutic patients and controls whom we have examined previously (Jonxis and Huisman, 1954). The plasma concentration of the different amino-acids, except those of tyrosine and phenylalanine, did not differ much from those found in our previously published cases of normal and scorbutic children, and the excretion of the other alpha-amino acids was much the same whether the phenylalanine and tyrosine had been administered or not. Although the evaluation of the results is difficult, because the values that are being compared are obtained from different patients, the differences between the normal and scorbutic children are so striking that we believe that certain conclusions may be drawn from the collected data.

Table 2 makes it clear that during the phenylalanine and tyrosine administration Case 1 was excreting the same amino-acids (tyrosine, serine, glycine, histidine, lysine, β-amino-isobutyric acid and also taurine) in about the same increased amount

TABLE 3

AMINO-ACID COMPOSITION OF PLASMA ULTRAFILTRATES OF NORMAL AND SCORBUTIC CHILDREN BEFORE AND DURING ADMINISTRATION OF DL-PHENYLALANINE AND L-TYROSINE*

Amino-acid	Scorbutic Infants			Controls		
	Mean of Two Patients (1)	Phenylalanine Load in Case 2	Tyrosine Load in Case 3	Mean of Two Normal Children (1)	Phenylalanine Load	Tyrosine Load
Taurine	5·0	7·5	8·5	5·0	5·5	4·5
Aspartic acid	1·5	4·0	6·5	1·0	3·0	4·0
Threonine	17·0	22·0	20·5	12·5	10·0	9·5
Serine	—	49·0	37·5	—	22·0	26·0
Glutamic acid	16·0	16·5	13·0	10·5	14·5	13·5
Proline	24·5	—	—	16·5	17·5	27·0
Glycine	16·0	20·5	24·5	14·0	15·5	11·0
Alanine	36·0	45·5	37·5	28·0	32·5	37·0
Cystine	—	10·0	5·0	—	10·5	22·0
Valine	23·0	31·5	30·0	20·0	28·0	30·5
Methionine	6·5	6·0	4·5	18·0	5·5	6·0
Isoleucine	9·5	14·5	10·0	8·0	11·0	15·5
Leucine	17·0	25·0	13·0	14·5	16·0	18·5
Tyrosine	15·0	45·5	79·5	15·5	53·0	165·0
Phenylalanine	13·5	144·0	19·0	19·0	318·5	17·0
Lysine	26·0	26·0	23·5	20·0	17·0	18·5
Histidine	10·0	10·5	10·5	15·0	13·5	11·5
Arginine	8·0	—	—	10·0	—	—

* Values given in mg./1,000 ml.

TABLE 4

EXCRETION OF DIFFERENT METABOLITES OF PHENYLALANINE AND TYROSINE BEFORE AND DURING ADMINISTRATION

Compound	Scorbutic Infant (Case 1)			Normal Control		
	Control Period	During Phenylalanine Load	During Tyrosine Load	Control Period	During Phenylalanine Load	During Tyrosine Load
Phenylalanine	8·0	2,235·0	25·0	3·0	1,850·0	8·0
Tyrosine	32·0	56·5	251·0	10·0	9·5	51·0
Tyrosyl compounds expressed as tyrosine	67·0	330·0	1,617·0	51·0	119·0	198·0
Keto-acids expressed as phenylpyruvic acid ..	19·0	261·0	96·0	21·0	141·0	46·5
Homogentisic acid	9·5	16·5	14·5	8·0	26·0	9·0

as the previously described scorbutic patients (see Table 2, first column). During the DL-phenylalanine load both the normal control and the patient were excreting much more phenylalanine, about 20% of the administered doses. The patient was excreting perhaps somewhat more than the control. It is known that the reabsorption of D-phenylalanine in the kidney tubule is limited. There was no marked influence of the phenylalanine load on the excretion of the other amino-acids except that in Case 1 the tyrosine excretion was somewhat high.

The results obtained during the L-tyrosine load show greater changes. In the control the excretion of tyrosine rose to 50 mg. The excretion of phenylalanine remained low. In Case 1, however, the tyrosine excretion rose to about 250 mg. and at the same time the excretion of phenylalanine rose to 25 mg. In the control child the phenylalanine excretion after the tyrosine administration was 8 mg.

From the results shown in Table 3 it is seen that the administration of tyrosine or phenylalanine did not alter significantly the concentration of the other amino-acids in the plasma. As was expected, the plasma levels of tyrosine and phenylalanine were high during the administration of these amino-acids but less so in the scorbutic child than in the control. The administration of phenylalanine also affected the plasma level of tyrosine in both the patient and control. In both there was a rise from about 15 to 50 mg. per 1,000 ml. The administration of tyrosine hardly affected the plasma level of phenylalanine in either the patient or the control. The higher tyrosine excretion during the tyrosine load in scorbutic child 1 is not, therefore, likely to have been caused by a higher plasma level of tyrosine (see plasma, Case 3). On the contrary the concentration of tyrosine in the plasma of Case 3 was lower than that of the control child during the tyrosine load. A diminished reabsorption of tyrosine is the most likely explanation of the increased excretion of tyrosine in the scorbutic child. Since the phenylalanine was administered in the DL form the conclusions about phenylalanine are less clear than those for tyrosine, but again the plasma levels were lower in Case 2 than in the control. Neither tyrosine nor phenylalanine were excreted in sufficiently large amounts during their respective administrations to make excretion seem likely to be the main cause of the lower plasma levels of these amino-acids in the scorbutic children. The fact that during the administration of phenylalanine the tyrosine level of the plasma was somewhat raised, in the scorbutic as well as in the control, but not the phenylalanine level during the tyrosine administration, can be explained by the fact that phenylalanine is converted into tyrosine and not conversely. This may explain the increased tyrosine excretion during the phenylalanine administration in the scorbutic child.

Table 4 shows the results of the determination of different metabolites of tyrosine and phenylalanine in the urine of the normal control and of Case 1. The scorbutic child excreted these metabolites in normal amounts. During the phenylalanine administration the excretion increased more in the scorbutic child than in the control, but the difference was not very great. When tyrosine was given the excretion of tyrosyl compounds rose about ten times as much in the scorbutic child as in the control. This effect has already been described by Rogers and Gardner (1949). It is noteworthy that the excretion of these tyrosyl substances (mainly para-hydrophenyllactic acid) is caused by the administration of tyrosine and not by that of phenylalanine. This is in accordance with the theory that in scurvy there is an impairment in the turnover of para-hydroxyphenylpyruvic acid into 2-5 dihydroxyphenylpyruvic acid.

Summary

DL-phenylalanine and L-tyrosine were administered by mouth to three scorbutic children, and the excretion in the urine and the plasma levels of these

and other amino-acids were determined. Both with and without additional tyrosine the excretion of tyrosine by scorbutic children was found to be much higher than by normal children. Since the plasma levels of phenylalanine and tyrosine were found to be low during the administration of these amino-acids, this amino-aciduria is thought likely to be of renal origin. As it has already been described by other authors the excretion of tyrosine substances is greatly increased in scorbutic children after the oral administration of tyrosine.

References

Felix, K. and Schaefer, H. (1950). *Hoppe-Seyl. Z. physiol. Chem.*, 286, 38.

——, Leonhardi, G. and Glasenapp, I. von (1951). *Ibid.*, **287**, 133.

Huisman, T. H. J. (1954). *Pediatrics*, **14**, 245.

Jonxis, J. H. P. and Huisman, T. H. J. (1954). *Ibid.*, **14**, 238.

—— and Wadman, S. K. (1950). *Maandschr. Kindergeneesk.*, **18**, 251.

Levine, S. Z., Gordon, H. H. and Marples, E. (1941). *J. clin. Invest.*, **20**, 209.

Medes, G. (1932). *Biochem. J.*, **26**, 917.

Moore, S. and Stein, W. H. (1954). *J. biol. Chem.*, **211**, 893.

Morris, J. E., Harpur, E. R. and Goldbloom, A. (1950). *J. clin. Invest.*, **29**, 325.

Neuberger, A. (1947). *Biochem. J.*, **41**, 431.

Rogers, W. F., Jr. and Gardner, F. (1949). *J. clin. Invest.*, **28**, 806.

Salmon, R. J. and May, C. D. (1950). *J. Lab. clin. Med.*, **36**, 591.

——, —— (1953). *Ibid.*, **41**, 376.

Sealock, R. R. and Silberstein, H. E. (1940). *J. biol. Chem.*, **135**, 251.

Stein, W. H., Bearn, A. G. and Moore, S. (1954). *J. clin. Invest.*, **33**, 410.

Van Slyke, D. D., Dillon, R. T., MacFadyen, D. A. and Hamilton, P. (1941). *J. biol. Chem.*, **141**, 627.

Woodruff, C. W. (1950). *J. Lab. clin. Med.*, **36**, 640.

THE ELECTROLYTE CONTENT OF THE SWEAT IN FIBROCYSTIC DISEASE OF THE PANCREAS

BY

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A diagnosis of fibrocystic disease of the pancreas is usually based on the following clinical criteria: failure to grow at the normal rate despite an adequate calorie intake, the passage of frequent loose, offensive stools often with a characteristic odour, and the tendency to respiratory tract infections which prove unusually resistant to treatment. These symptoms, together with a finding that pancreatic enzyme activity is absent in samples of duodenal juice obtained by intubation, establish the diagnosis. The collection of adequate samples of duodenal juice for analysis may prove tedious both for the ward and the patient and an alternative diagnostic procedure of greater simplicity would be an advantage. The concept of fibrocystic disease has undergone some change in recent years and it is now generally agreed that it is a disease of mucus and non-mucus secretory glands. One of the most interesting developments is that the electrolyte content of sweat and saliva may be abnormal in patients with the condition. It was observed (Di Sant'Agnese, Darling, Perera and Shea, 1953) that levels of sodium above 80 m.Eq. per litre and chlorides above 60 m.Eq. per litre in the sweat were diagnostic of fibrocystic disease. Similar results for the electrolyte content of sweat in fibrocystic disease have been recently reported by Finch (1956). The present paper confirms that the sweat electrolytes are abnormally high in known cases of the disease and describes a convenient technique for the collection and analysis of specimens of sweat.

Experimental

Material. Specimens of sweat were obtained from 12 patients with fibrocystic disease, varying in age from 11 months to 6 years. All 12 were proven cases in each of which pancreatic enzymes had been shown to be absent by at least one duodenal intubation. The control series consisted of 20 ward patients, varying in age from 3 months to 6 years, with no disease or symptoms referable to the gastro-intestinal tract.

Collection of Specimens. The ward was supplied with two weighed plastic tubes with close-fitting plastic stoppers (weight about 6 g.) each containing a single circular piece (7 cm. diameter) of Whatman No. 42 filter paper and two plastic sheets (approximately 10 cm. square). The plastic tubes and sheets had been previously washed with soap and water, then distilled water and finally dried at 37° C. for 24 hours. A box of clean filter papers was also included together with a bottle of distilled water, waterproof adhesive plaster, forceps and scissors. The equipment is illustrated in Fig. 1. The plastic squares were joined by means of a single strip of waterproof plaster which was then fixed to the spine, the filter papers being placed underneath the plastic squares and the whole secured with further strips of plaster (Fig. 2). The back was previously cleaned several times with filter papers soaked in distilled water and carefully dried. All these manipulations were performed with the clean forceps, and care was taken to place the filter papers symmetrically either side of the spine and as far as possible in similar areas in the different patients. The axillae were avoided because the apocrine secretion differs in its electrolyte composition. The patient was then placed in a plastic bag tied loosely with tapes around the neck (Fig. 3) and allowed to lie in a cot or bed covered with three or four blankets. In some instances the children were restive at first but quickly became used to the conditions. Experience showed that sufficient sweat had been absorbed by the filter papers when the inside of the bag became visibly wet, usually within one to two hours. Any gross contamination of the fluid inside the bag with urine was obvious. The

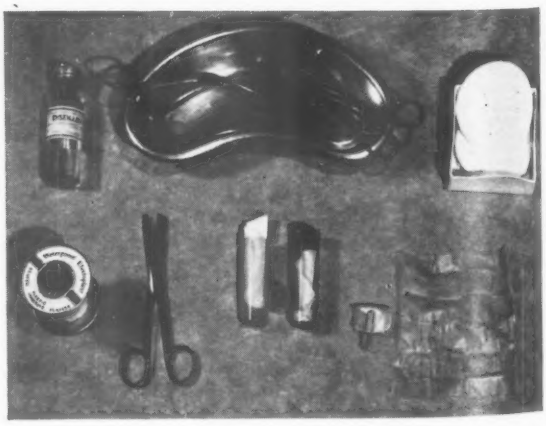

FIG. 1.—Equipment for collection of specimens of sweat.

FIG. 2.—Mode of attachment of filter papers and plastic strips to child.

plaster and plastic strips were then removed and the filter papers transferred to the plastic containers with the forceps and immediately taken to the laboratory.

Analysis of Specimens. The plastic containers and filter papers were reweighed, the increase in weight being the amounts of sweat collected (usually 0·5 to 2·0 g.), 5 ml. of glass-distilled water were added to each container and the mixtures shaken until the filter papers had disintegrated to a pulp. After passage through a sintered glass filter to produce an optically clear filtrate, chloride was estimated by the method of Schales and Schales (1941) which involves a direct titration with standard mercuric nitrate solution using diphenylcarbazone as an indicator. A further 1 ml. of the filtrate was diluted suitably, e.g., 1 to 50, the actual dilution being based on the chloride content of the specimen, for the estimation of sodium by the flame photometer. The results were calculated as m.Eq. of chloride or sodium per litre of sweat. The use of two pieces of filter paper enabled duplicate estimations to be performed on each patient.

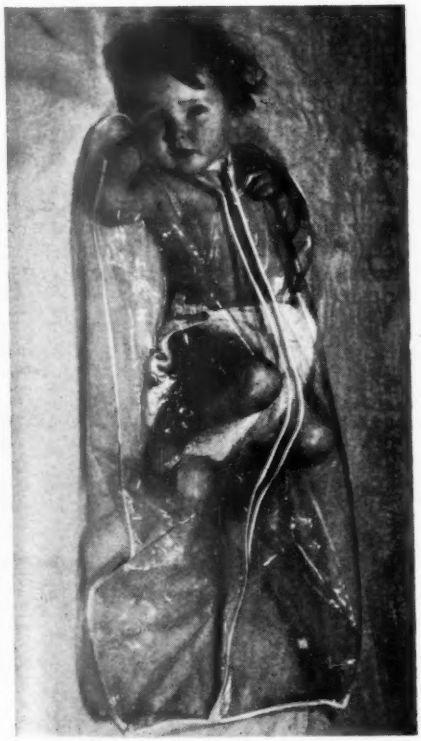

FIG. 3.—Plastic bag in position.

Results

Table 1 gives the results for 20 controls and Table 2 those for 12 patients with fibrocystic disease.

TABLE 1
ELECTROLYTE CONTENT OF SWEAT IN 20 CONTROL PATIENTS

Case No.	Age	Sex	Electrolyte Content of Sweat (m.Eq./litre)	
			Sodium	Chloride
1	3 months	M	25	24
2	3 months	M	32	31
3	4 months	F	16	14
4	4 months	M	11	12
5	7 months	M	13	18
6	8 months	F	37	38
7	11 months	M	19	17
8	11 months	F	29	25
9	1 year	F	52	40
10	14 months	F	33	27
11	18 months	F	4	9
12	2 years	M	16	17
13	2 years	M	40	40
14	2 years	F	48	25
15	3 years	M	25	20
16	4 years	F	19	9
17	5 years	M	23	16
18	5 years	F	34	28
19	5 years	F	35	36
20	6 years	F	27	20
Mean ± standard deviation ..			27±12	23±10
Range			4 – 52	9 – 40

TABLE 2
ELECTROLYTE CONTENT OF SWEAT IN 12 PATIENTS WITH FIBROCYSTIC DISEASE

Case No.	Age	Sex	Electrolyte Content of Sweat (m.Eq./litre)	
			Sodium	Chloride
1	11 months	F	142	144
2	2 years	F	106	128
3	3 years	M	72	68
4	3 years	M	143	148
5	4 years	M	128	125
6	4 years	M	119	127
7	4 years	M	138	136
8	5 years	F	126	126
9	6 years	M	157	145
10	6 years	F	135	141
11	7 years	F	95	95
12	7 years	M	138	136
Mean ± standard deviation ..			125 ± 24	127 ± 23
Range			72 – 157	68 – 148

TABLE 3

COMPARISON OF ELECTROLYTE CONTENT OF SWEAT IN CONTROLS AND PATIENTS WITH FIBROCYSTIC DISEASE

Reference	Controls			Fibrocystic Patients		
	No. of Cases	Sodium (m.Eq./l.)	Chloride (m.Eq./l.)	No. of Cases	Sodium (m.Eq./l.)	Chloride (m Eq./l.)
Di Sant'Agnese *et al.* (1953) ..	50	59 10–120	32 4–80	43	133 80–190	106 60–160
Finch (1956)	30	27 7·7–59	18 trace–50	6	107 86–132	108 85–138
Present work	20	27 4–52	23 9–40	12	125 72–157	127 68–148

The statistical significance of the differences between the mean results for sodium and chloride of the controls and fibrocystic patients were analysed by Student's t test and values of P of $<0{\cdot}001$ were obtained in each case. Table 3 includes the results of the present work together with the figures reported by other workers.

Discussion

The results of the present work fully confirm the report of Di Sant'Agnese *et al.* (1953) that the estimation of sodium and chloride in sweat is very useful in the diagnosis of fibrocystic disease. In our series there was a highly significant statistical difference between the content of these two electrolytes in the sweat specimens from the controls and from the fibrocystic cases. It may be concluded that sodium and chloride levels above 70 m.Eq. per litre in sweat specimens, collected according to the method described in the experimental section above, together with typical clinical findings, are diagnostic of fibrocystic disease. However, adherence to the details of collection is important in that the electrolyte content of sweat in any individual varies with a number of factors such as the area of collection, nature and intensity of the stimulus to sweating, environmental temperature, dietary intake and adrenocortical activity. We have attempted to devise a reasonably standard and simple procedure which could be used in most hospital wards. The method differs from the technique of Di Sant'Agnese *et al.* (1953) mainly in the use of filter papers and plastic containers instead of pads of gauze and glass vessels. This modification enables the weight of the sweat specimen to be more accurately measured because it is a greater fraction of the total weight of the containers. The chemical analyses are simple and we consider that the method is a desirable alternative to duodenal intubation in which the difficulties of collection and analysis of the specimens are much greater. It is of interest that when the purpose of the test was being explained several parents of the fibrocystic patients commented on the salty sensation experienced when kissing their children.

Summary

A method for the collection of specimens of sweat is described and the sodium and chloride content of sweat from control subjects and fibrocystic patients have been measured.

The electrolyte content of sweat from fibrocystic patients is significantly higher than that of sweat from the control subjects.

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REFERENCES

Di Sant'Agnese, P. A., Darling, R. C., Perera, G. A. and Shea, E. (1953). *Pediatrics*, **12**, 549.

Finch, E. (1956). Communication to the Association of Clinical Biochemists, Midland Region.

Schales, O. and Schales, S. S. (1941). *J. biol. Chem.*, **140**, 879.

KERNIKTERUS NOT ASSOCIATED WITH HAEMOLYTIC DISEASE

BY

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Kernikterus (bile staining of brain nuclei at necropsy or jaundice causing neurological signs during life) not associated with haemolytic disease has been reported in the literature during the last few years. Black-Schaffer, Kambe, Furuta and Moloney (1954) described 13 cases which had died with kernikterus in Hiroshima during the neonatal period. Eleven of the 13 cases were premature infants. Aidin, Corner and Tovey (1950) likewise described 24 cases of kernikterus of which 23 were premature infants. Crigler and Najjar (1952) described a case of kernikterus in a family with an inherited bilirubin excretion defect in the liver, and Ehrlich and Ratner (1955) described a case of kernikterus in an infant with ' neonatal hepatitis'. Most of the published cases dealt with premature infants, but in the following series it will be shown that kernikterus in full-term infants not associated with iso-immunization is quite common in Singapore.

During the period from March, 1955, to December, 1955, 96 cases of jaundice during the first year of life were admitted to the Paediatric Unit of the General Hospital. In all these cases, the blood of the infant was tested for Rh and ABO antibodies and the Coombs antiglobulin test was done, but only two cases were found to be caused by iso-immunization (one due to Rh incompatibility and one due to ABO incompatibility). There were, however, 26 cases showing the symptoms, signs or pathological lesions of kernikterus. These 26 infants were all full term, under the age of 15 days on admission, and showed no evidence of iso-immunization. The criteria for diagnosis of these cases were a high serum bilirubin level with or without severe jaundice, with neurological signs, and evidence of bile-staining in the brain nuclei at necropsy in those who died. In more than half of the 26 cases the serum bilirubin was estimated after the manner of Hsia and his colleagues' modification of Evelyn and Malloy's method. The one-minute value corresponds to the 'direct-bilirubin', the normal for which is 0-0·2 mg. % for all ages, and the 30-minute value is the 'indirect-bilirubin', the normal for which one week after birth is less than 0·8 mg. %.

Clinical Features

The clinical features of these 26 cases resembled each other quite closely and a random selection of the case histories and the findings of a few of them will now be given.

Case 1. Y.Y.C., a 6-day-old Chinese baby girl, was admitted on May 16, 1955, with a history of fever with jaundice for one day before admission. She was the second child born at full term by normal delivery with a birth weight of 7 lb. The first child is alive and well. On examination she had a temperature of 101° F. with severe jaundice and extensive thrush in the mouth. The liver was palpable one fingerbreadth, but the spleen was not felt. The limbs were stiff and the child had occasional fits. Investigations revealed the following: Haemoglobin 80% (Sahli); the peripheral blood showed no normoblasts; reticulocyte count 0·8%; serum bilirubin level 32·5 mg. per 100 ml.; a blood Kahn test of the mother and infant was negative; both mother and infant were Rhesus positive, group B; the Coombs test was negative; no abnormal agglutinins were detected in the blood. The thrush infection was treated, the temperature subsided and the child survived. The jaundice disappeared completely after four months but the limbs were still slightly stiff and the milestones delayed. The child is still under observation.

Case 15. L.B.H., a 10-day-old Chinese baby boy, was admitted on April 10, 1955, with a history of jaundice noticed on the third day of life and diarrhoea for four days before admission. He was the third child, and was born at full term with a normal delivery and a birth weight of 6 lb. 13 oz. The other two children are alive and well. On examination, he had a temperature of 99° F. with severe jaundice and slight dehydration. The throat was injected and the umbilicus was septic. The liver was palpable one and a half fingerbreadths, but the spleen was not felt. Investigation revealed the following:

Red cells 6·02 million, Hb 123%. The peripheral blood showed no normoblastic reaction. The blood Kahn reactions of the mother and infant were negative. Both mother and infant were Rh positive but the mother was group O while the child was group A; the Coombs test was negative and no abnormal agglutinins were detected. The child died the next day and necropsy showed bright yellow staining of the basal nuclei.

Case 27. S.P.Y., 10-day-old Chinese baby boy, was admitted on June 1, 1955, with a history of jaundice one day after birth and one day before admission he had fever with dyspnoea. He was the first child, born at full term with a normal delivery and a birth weight of 8 lb. 3 oz. On examination he had a temperature of 101° F. with intense orange-yellow jaundice and a septic umbilicus. The liver was palpable one fingerbreadth but the spleen was not palpable. The peripheral blood showed no normoblastic reaction. The serum bilirubin level at 1 min. was 5·8 mg. %, at 30 min. 35·6 mg. The cephalin-cholesterol flocculation test was strongly positive. The blood Kahn reactions of mother and infant were negative. Both mother and child were Rh positive, group A. The Coombs test was negative and no abnormal agglutinins were detected. The child died the next day and necropsy showed bile-staining of the brain nuclei.

Case 43. Q.A.K., a 7-day-old Chinese baby girl, was admitted on July 10, 1955, with a history of jaundice one day after birth and fever with refusal of feeds one day before admission. She was the second child, born at full term with a normal delivery and a birth weight of 5 lb. 2 oz. The first child is alive and well. On examination she had a temperature of 100° F. with severe jaundice. The liver was palpable one fingerbreadth below the costal margin but the spleen was not palpable. The peripheral blood showed no normoblastic reaction. The serum bilirubin level at 1 min. was 0·5 mg. %, at 30 min. 43·0 mg. %. The cephalin-cholesterol flocculation test was negative. The mother was Rh positive, group A, while the infant was Rh positive, group B. The Coombs test was negative, and no abnormal agglutinins were detected. She died the same day and necropsy revealed kernikterus.

An analysis of the more common symptoms which brought the infants to hospital is shown in Table 1.

From the above, it is seen that in all of the 26 cases, there was a complaint of refusal of feeds, 73% had fever, 42·3% had vomiting, 19·2% presented with breathlessness and 15·4% had fits.

It is seen that every case exhibited jaundice, 73% of them were drowsy, 61·5% had manifest concomitant infection, 46·1% had stiffness of limbs or neck and 7·7% were in different degrees of dehydration. In nearly all the cases the liver was palpable below the costal margin but this finding in itself is not of much significance because, in Singapore,

TABLE 1
PRESENTING SYMPTOMS

No.	Case No.	Fever (73%)	Refused Feeds (100%)	Vomiting (42·3%)	Dyspnoea (19·2%)	Fits (15·4%)
1	1	+	+	−	−	−
2	10	−	+	+	−	−
3	13	+	+	+	−	−
4	15	−	+	−	−	−
5	17	+	+	−	−	−
6	18	+	+	−	−	−
7	22	+	+	−	−	−
8	23	+	+	−	−	−
9	24	+	+	+	−	−
10	27	+	+	−	+	−
11	35	−	+	+	−	+
12	37	+	+	+	+	−
13	43	+	+	−	−	−
14	47	+	+	−	−	−
15	50	+	+	+	+	−
16	59	+	+	−	+	−
17	71	−	+	−	−	−
18	73	−	+	−	−	−
19	76	+	+	+	−	−
20	80	+	+	+	−	−
21	81	+	+	−	−	+
22	82	+	+	+	−	−
23	84	−	+	+	−	−
24	85	+	+	+	+	−
25	86	−	+	−	−	−
26	88	+	+	−	−	−

infants in the neonatal period invariably have palpable livers. In only four out of the 26 cases was the spleen palpable.

Tables 2 and 3 set out further data on the series. In Table 3, we see that 23 out of the 26 cases are Chinese. This is probably of no significance since the population of Singapore is predominantly Chinese and most of the admissions to the Unit are from the same race. The other three consist of Malay infants. Females number 12, while there are 14 males. The ages of those who died and at necropsy revealed kernikterus varied from 5 to 13 days. In five of these 26 cases the birth weight was not available, but in the remaining 21 cases all the birth weights were above 5 lb. and all were delivered at full term except for two babies whose gestation periods were 36 weeks. In Singapore the definition of prematurity includes infants weighing 5 lb. or less at birth, so that all the 21 cases would be considered mature in this series. The day when jaundice was first noticed varied from one to six days after birth. In those cases where the serum bilirubin level was estimated, the 30-minute value ranged from 23 mg. % to 54 mg. %. In all the 26 cases, serology did not reveal any Rh or ABO incompatibility. The Coombs test was negative and no abnormal agglutinins were detected.

Histological sections were made of the livers and Professor R. Kirk examined them and reported as follows in three of the post-mortem cases:

Case 59. There is diffuse fatty change throughout the whole liver. The sinuses are greatly congested with

TABLE 2

CLINICAL FINDINGS ON ADMISSION

No.	Case No.	Age in Days on Admission	Infection (61·5%)	Jaundice (100%)	Muscular Hypertonicity (46·1%)	Drowsiness	Dehydration	Liver	Spleen
1	1	6	Thrush	+	+	+	−	1 f.b.	n.p.
2	10	4	—	+	−	+	−	2 f.b.	n p.
3	13	3	Conjunctivitis	+	+	+	−	½ f.b.	n.p.
4	15	10	Of umbilicus	+	−	+	+	1½ f.b.	n.p.
5	17	9	Conjunctivitis	+	−	−	−	2 f.b.	n.p.
6	18	6	—	+	−	−	−	½ f.b.	1 f.b.
7	22	4	Thrush	+	−	+	−	2 f.b.	n.p.
8	23	6	Of umbilicus	+	−	+	−	2 f.b.	n.p.
9	24	11	Pharyngitis	+	−	+	+	2 f.b.	n.p.
10	27	10	Of umbilicus	+	−	+	−	1 f.b.	n.p.
11	35	6	Of umbilicus	+	+	+	−	1 f.b.	n.p.
12	37	3	Of umbilicus	+	−	+	−	1 f.b.	n.p.
13	43	7	—	+	−	+	−	1 f.b.	n.p.
14	47	5	Pharyngitis	+	+	−	−	1 f.b.	n.p.
15	50	12	Of umbilicus	+	−	+	−	½ f.b.	n.p.
16	59	11	—	+	−	+	−	n.p.	n.p.
17	71	6	Pneumonia	+	+	+	−	n.p.	n.p.
18	73	7	—	+	+	+	−	1 f.b.	n.p.
19	76	6	Pneumonia	+	−	−	−	1 f.b.	n.p.
20	80	8	Pharyngitis	+	+	−	−	2 f.b.	1 f.b.
21	81	14	—	+	+	−	−	1 f.b.	n.p.
22	82	5	—	+	+	+	−	1 f.b.	n.p.
23	84	3	—	+	+	−	−	½ f.b.	½ f.b.
24	85	8	—	+	+	+	−	3 f.b.	n.p.
25	86	3	—	+	−	+	−	1 f.b.	½ f.b.
26	88	6	Of umbilicus	+	+	+	−	1 f.b.	n.p.

+ = positive
− = negative
n.p. = not palpable
f.b. = fingerbreadth

TABLE 3

FURTHER DATA ON THE SERIES

No.	Case No.	Age in Days		Sex	Race	Alive (A) or Died (D)	Day after Birth when Jaundice First Noticed	Birth Weight (lb. oz.)	Period of Gestation	Serum Bilirubin (mg. per 100 ml.)		Hb % (Sahli)	Cephalin-Cholesterol Liver Function Test
		On Admission	At Death							1 min.	30 min.		
1	1	6	—	F	C	A	5	7 0	Full term	6·6	32·5	80	*
2	10	4	5	M	C	A	2	†	†	*	*	75	*
3	13	3	5	M	C	D	2	5 0	Full term	*	*	75	*
4	15	10	10	M	C	D	3	6 3	Full term	*	*	120	*
5	17	9	9	F	C	D	1	6 12	Full term	*	*	*	*
6	18	6	7	F	C	D	3	6 10	Full term	*	*	125	*
7	22	4	5	M	C	D	2	5 0	36 wk.	*	*	*	*
8	23	6	6	M	C	D	4	8 3	Full term	*	*	*	*
9	24	11	12	F	C	D	6	7 0	Full term	*	*	*	*
10	27	10	11	M	C	D	1	8 6	Full term	5·8	35·6	*	++++
11	35	6	8	F	M	D	4	†	†	8·3	30·0	140	Negative
12	37	3	5	M	C	D	1	7 8	Full term	5·0	28·8	80	Negative
13	43	7	8	F	C	D	1	5 2	Full term	0·5	43·0	*	Negative
14	47	5	—	F	M	A	4	7 0	Full term	12	37	*	Negative
15	50	12	13	F	C	D	2	6 3	Full term	2	23	*	++
16	59	11	11	M	C	D	†	†	†	*	*	*	*
17	71	6	7	M	C	D	2	6 0	Full term	*	*	*	*
18	73	7	8	M	C	D	1	†	36 wk.	*	*	*	*
19	76	6	6	M	C	D	†	†	†	*	*	*	*
20	80	8	—	F	C	A	6	6 0	Full term	10	37·5	88	Negative
21	81	14	—	F	C	A	3	6 1	Full term	*	*	*	*
22	82	5	5	M	C	D	1	7 4	Full term	*	*	*	*
23	84	3	—	F	M	A	2	7 4	Full term	9·4	54	78	Negative
24	85	8	9	F	C	D	1	7 4	Full term	3·2	48	*	*
25	86	3	5	M	C	D	1	7 0	Full term	0	23	92	*
26	88	6	—	M	C	A	5	9 0	Full term	4·5	47·8	70	Negative

* = Not done
† = Not known
C = Chinese
M = Malay

blood, showing many nucleated red cells. The portal tracts show early diffuse infiltration with mononuclear cells. The architecture of the liver structures is normal and well maintained.

Case 85. Some diffuse fatty change. The portal tracts are infiltrated with cells and in places show an excessive amount of fibrous tissue. The liver cells stain very irregularly and the infiltration, mainly of mononuclear cells, extends inwards from the portal tracts into the substance of the liver lobules. Congestion not specially marked but nucleated red cells noticeable.

Case 43. The portal tracts are infiltrated with mononuclear cells. The liver cells show diffuse fatty change. Congestion not specially marked. Some nucleated red cells are visible.

He summarizes the findings thus: ' There is nothing specific in these findings. The only constant pathological change is the fatty change seen in the livers.

' The presence of nucleated red cells in the vessels and sinuses is probably due to the continued haemopoiesis there and not to erythroblastosis foetalis as this condition is definitely excluded by the blood examination in these cases.'

Discussion

The Cause of Kernikterus. Most of the theories of the causation of kernikterus can be summarized into two main groups: (1) The concept that the brain is damaged first and then some form of bilirubin is fixed in these injured tissues; (2) that bilirubin and its products damage the brain nuclei themselves.

The proponents of the first theory considered birth trauma, anaemia, cerebral anoxia, vascular occlusions, etc., as the damaging aetiological agent. In the present series there was no evidence of birth trauma and delivery had been normal. The infants were delivered either in the Kandang Kerbau Maternity Hospital or by qualified midwives in the mothers' own homes. The haemoglobin level in our series showed that whenever it was estimated it had never been below 70% (100% = 14·8 g. Hb). Claireaux's (1950) figures for his infants with kernikterus ranged from 120% to 70%. Pickles (1949) has pointed out that in the most anaemic newborn and stillborn infants with hydrops foetalis resulting from haemolytic disease of the newborn there was no jaundice or any signs of bile staining of the brain nuclei. The argument that premature babies are more prone to kernikterus than full-term infants due to their greater liability to cerebral anoxia and hence brain damage is not really tenable; according to Smith (1951), in animal experiments, newborn animals can survive anoxia for periods 40 times as long as adults, and the more premature the animal, the more resistant it is to anoxic effects. This resistance is probably due to the relatively more anaerobic carbohydrate metabolism in the foetal stage being carried over into the neonatal period. The strongest evidence against a pre-injury to the brain is the well-established observation that exchange transfusions if done early enough bring about total recovery with no neurological sequelae in cases of haemolytic disease of the newborn.

It is therefore more likely that bilirubin or its products in excessive amounts in the blood are deposited in the brain tissue and cause the injury directly. Najjar, quoted by Black-Schaffer *et al.* (1954), advances the theory that the bilirubin molecule is an analogue of heme and may in this sense be able to compete with heme at the active surface of the heme-containing enzymes, such as cytochromes, and may produce damage to the brain cells.

Accepting the theory that kernikterus in the newborn may be caused by a bilirubinaemia, the question arises as to what level the bilirubin should rise in the blood before it passes the blood-brain barrier. Mollison and Cutbush (1954) found that with plasma concentrations of total bile pigment of 19 to 24 mg. per 100 ml. one baby in 13 suffered brain damage, and that this is increased to four out of 12 if the amount of pigment rose to 24 to 29 mg. per 100 ml. Above that amount, the majority of infants were affected. Hsia, Allen, Gellis and Diamond (1952) in their series of cases of haemolytic disease of the newborn considered that approximately 50% of those infants with a serum bilirubin level of more than 30 mg. per 100 ml. are liable to kernikterus. In our present series, kernikterus occurred when the serum bilirubin level was definitely high. The lowest was 23 mg. % and the highest 54 mg. % (Fig. 1) in the 12 cases where the serum bilirubin was estimated. The serum bilirubin could not be estimated in the rest because they were admitted *in extremis*.

The type of bilirubin causing kernikterus is the 'indirect form' which in our series is represented by the '30-minute bilirubin'. But the actual type of pigment which is deposited in the kernikteric brains has not been definitely established. Vogel (1953) extracted the pigment from the brains of three infants dying of kernikterus and showed by electrophotometry that it resembled crystalline mesobilirubin.

Cause of Kernikterus in Present Series. In the present series, haemolytic disease was excluded by all available methods, and none of the 26 cases were premature by weight and only two were immature

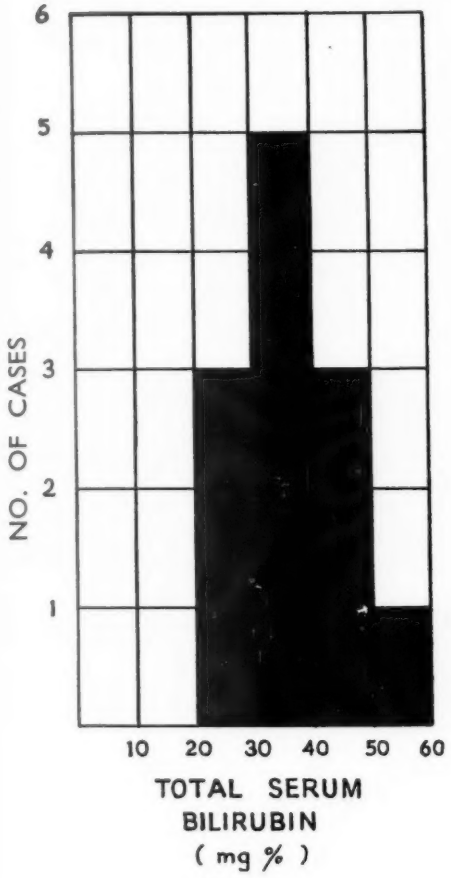

FIG. 1.

by gestation period. It may be significant that 61·5% had demonstrable foci of infection, which may affect the liver, producing a toxic hepatitis, and when this is associated with the immature liver of the newborn and the physiological excessive breakdown of red cells, then an excess of bilirubin will accumulate in the blood. However, it will be noted that the age of onset of the jaundice in 14 out of our 26 cases was in the first two days of life which is very early for a toxic hepatitis from sepsis.

We also considered the possibility of a virus infection of the liver, and a few samples of blood from these cases were injected into mice by Dr. K. A. Lim, but no conclusive results were obtained. Stokes, Berk, Malamut, Drake, Barondess, Bashe, Wolman, Farquhar, Bevan, Drummond, Maycock, Capps and Bennett (1954) had a case of 'viral hepatitis' in an infant where the serum of infant and mother was injected into human volunteers and 40-60% of the volunteers developed hepatitis after an incubation period varying from 74 to 100 days, and they considered that it is possible for an infant to be affected with viral hepatitis while *in utero*, i.e., a foetal viral hepatitis. Except for this single instance no further proof has been obtained and as the matter now stands this problem remains unsolved.

Stokes, Wolman, Blanchard and Farquhar (1951), Craig and Landing (1952), Dible, Hunt, Pugh, Steingold and Wood (1954), Gellis, Craig and Hsia (1954), and Ehrlich and Ratner (1955) have described cases of neonatal jaundice, and at necropsy a 'giant-cell cirrhosis' was found. In one of the two cases described by Ehrlich and Ratner, there was evidence of kernikterus at necropsy. In our cases, no evidence of 'giant-cell cirrhosis' was found.

All our cases were from the lower-income groups with mothers subsisting on suboptimal diets, and although we have not been able to go into the diets of the mothers thoroughly, interrogation usually revealed that their diet consisted of highly-polished rice, vegetables, with occasional fish and rarely any meat—a diet that is highly deficient in protein, and we wonder whether this poor diet may have resulted in infants being born with livers functioning inefficiently. Kwashiorkor in a mild form does exist in Singapore, and the majority of children coming to necropsy have fatty livers irrespective of the cause of death. Furthermore, the constant feature in the histological sections of the livers of the above cases was a diffuse fatty change. It could be that these infants were born with livers which were inefficient in dealing with the normal physiological bilirubinaemia as a result of protein malnutrition in the mothers.

Management. We find that once the stage of clinical kernikterus is reached, most of them die in spite of any treatment. Twenty-one out of the 26 cases died, with a mortality rate of 81%. If, as discussed above, the pathology resides in the liver, then a careful prophylactic diet should be advised for the mother. All infections in the newborn should be promptly treated before feeding difficulties and vomiting cause further depletion of liver resources. In one patient (Case 86), who was very ill, an exchange transfusion was carried out but the patient died.

Summary

Twenty-six cases of kernikterus of non-haemolytic origin in the newborn infant occurring in the Paediatric Unit of the General Hospital, Singapore, during the period March, 1955, to December, 1955, are described.

The incidence of these cases in full-term, mature infants as distinct from previous reports mainly in premature infants is stressed.

The mechanism of kernikterus in general is briefly described and the probable mode of the production of kernikterus in the present series discussed. It is suggested that in some of these cases the offending pigment, which is the 'indirect bilirubin', is excessively raised as a result of the normal physiological breakdown of red cells after birth superimposed on an inefficient liver due to protein malnutrition in the mother. Sepsis may have been a contributory factor.

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References

Aidin, R., Corner, B. and Tovey, G. (1950). *Lancet*, I 1153.
Black-Schaffer, B., Kambe, S., Furuta, M. and Molomey, W. C. (1954). *Amer. J. Dis. Child.*, **87**, 737.
Cathie, I. A. B. (1946). *Archives of Disease in Childhood* 21, 229.
Claireaux, A. (1950). *Ibid.*, **25**, 71.
Craig, J. M. and Landing, B. H. (1952). *A.M.A. Arch. Path.*, **54**, 321.
Crigler, J. F., Jr. and Najjar, V. A. (1952). *Pediatrics*, 10, 169.
Dible, J. H., Hunt, W. E., Pugh, V. W., Steingold, L. and Wood, J. H. F. (1954). *J. Path. Bact.*, **67**, 195.
Ehrlich, J. C. and Ratner, I. M. (1955). *Amer. J. Path.*, 31, 1013.
Gellis, S. S., Craig, J. M. and Hsia, D. Y-Y. (1954). *Amer. J. Dis. Child.*, **88**, 285.
—— and Hsia, D. Y-Y. (1955). *Pediat. Clin. N. Amer.*, p. 449.
Hsia, D. Y-Y., Allen, F. H., Jr., Gellis, S. S. and Diamond, L. K. (1952). *New Engl. J. Med.*, **247**, 668.
Lathe, G. H. (1955). *Brit. med. J.*, **1**, 192.
Mollison, P. L. and Cutbush, M. (1954). *Recent Advances in Paediatrics*, ed. D. Gairdner, p. 110. London.
—— and Walker, W. (1952). *Lancet*, **1**, 429.
Pickles, M. M. (1949). *Haemolytic Disease of the Newborn*. Oxford.
Smith, C. A. (1951). *The Physiology of the Newborn Infant*, 2nd ed., pp. 141-52. Springfield, Illinois.
Stokes, J., Jr., Wolman, I. J., Blanchard, M. C. and Farquhar, J. D. (1951). *Amer. J. Dis. Child.*, **82**, 213.
——, Berk, J. E., Malamut, L. L., Drake, M. E., Barondess, J. A., Bashe, W. J., Wolman, I. J., Farquhar, J. D., Bevan, B., Drummond, R. J., Maycock, W. d'A., Capps, R. B. and Bennett, A. M. (1954). *J. Amer. med. Ass.*, **154**, 1059.
Vogel, F. S. (1953). *Amer. J. Path.*, **29**, 582.
Weech, A. A. (1947). *Advances in Pediatrics*, vol. 2, p. 346. New York.
Zimmerman, H. M. and Yannet, H. (1933). *Amer. J. Dis. Child.*, **45**, 740.

HAEMOGLOBIN IN CORD BLOOD IN NORMAL AND PROLONGED PREGNANCY

BY

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There have been few investigations on the haemoglobin level in foetal blood at different stages of human pregnancy. While studying the oxygen saturation in cord blood (Rooth and Sjöstedt, 1957), we also measured the amount of haemoglobin in some infants.

Material

Four hundred and fourteen healthy infants born in the Department of Obstetrics and Gynaecology were investigated. In no case was pregnancy complicated by toxaemia. All infants were delivered spontaneously without complications in occipito-anterior presentation and they showed no signs of asphyxia. In order to obtain reliable information on the duration of gestation, the dates on menstrual age were carefully checked. Only cases with a regular menstrual cycle were included and any in which the duration of pregnancy was in doubt were excluded.

Techniques

Immediately after delivery the cord was clamped in two places and blood extracted from the vein. The haemoglobin was determined as oxyhaemoglobin in a Beckman C photoelectric colorimeter with an interference filter (Bausch and Lomb) of 575 mμ. The blood was diluted one part in 240 parts of 0·01% Na_2CO_3 solution. To calculate the amount of haemoglobin, a millimolecular extinction of 15·35 was used (Drabkin, 1946). The molecular weight of haemoglobin was assumed to be 68·000. The determinations were carried out by the Central Laboratory of the University Hospital, Lund, through the courtesy of Professor C. G. Holmberg and Dr. S. Hansson.

Results

The results of the haemoglobin estimations are summarized in Table 1. The mean of the determinations is 16·72 g. haemoglobin per 100 ml. blood, which agrees with those of other recent workers (Vahlquist, 1941; DeMarsh, Alt and Windle, 1948; Mollison, 1951; Dochain, Lemage and Lambrechts, 1952; Marks, Gairdner and Roscoe, 1955). Before the 38th week our determinations are too few for any reliable conclusions to be safely drawn. In the 38th week the haemoglobin value is 15·50 g. and in the 39th 16·31 g. In the 40th week the value is 16·98 and remains then at a constant level. Cord blood from the 42 cases with prolonged pregnancy, i.e., children born in the 43rd week or later, does not contain more haemoglobin than cord blood from infants born in the 40th, 41st or 42nd weeks. The mean value in the 43rd week is 16·92 g. and for the other three 17·07 g. per 100 ml.

Discussion

In 1953, Walker and Turnbull published a series of 145 cases in which pregnancy and labour were normal. They found that the haemoglobin level rose steadily from 9 g. per 100 ml. in the 10th week to 14 or 15 g. by the 22nd-24th week. By the 38th week the mean value was 15·2 g. and by the 40th week 16·5 g. When pregnancy was prolonged this rise continued and by the 43rd week the mean value was 18·8 g. Kravkova (1954) also found a rise in the haemoglobin level from the fourth to the tenth month. However, she did not

TABLE 1

HAEMOGLOBIN LEVEL IN CORD BLOOD OF HUMAN FOETUS

Duration of pregnancy in weeks ..	27	33	35	36	37	38	39	40	41	42	≥43	All
Haemoglobin (g. per 100 ml.) ..	11·8	16·2	16·8	15·2	15·9	15·50	16·31	16·98	17·36	16·67	16·92	16·72
Number	1	1	1	4	7	25	48	117	112	56	42	414

study any cases of prolonged pregnancy. Marks *et al.* (1955), studying 221 normal infants, were unable to confirm Walker and Turnbull's results, as they found no correlation between cord blood haemoglobin and the foetal gestation time. Our results are thus in accordance with those of Marks *et al.* since we find that the haemoglobin level is constant from the 40th to the 43rd week.

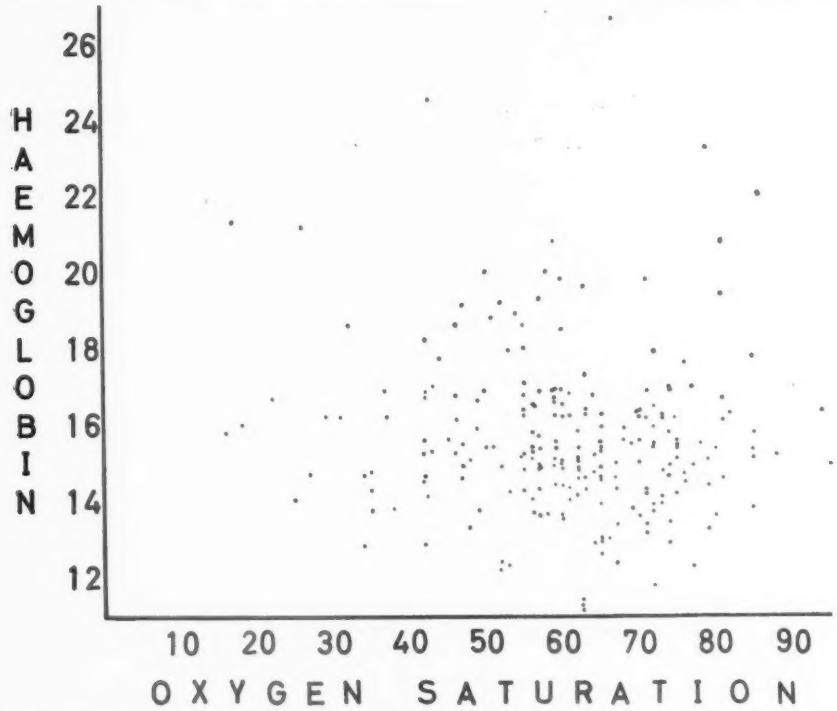

FIG. 1.—Scattergram of haemoglobin values of cord blood plotted against oxygen saturation of blood in the cord vein. Oxygen saturation in per cent., haemoglobin in g. per 100 ml.

The range in the cord blood haemoglobin is from 11·2 g. to 26·6 g. per 100 ml. Like Marks *et al.*, we observed a wide range in our values, whereas Walker and Turnbull state that the haemoglobin varies relatively little within the weeks.

Walker and Turnbull conclude that the rise in the haemoglobin level seen in late pregnancy is a response by the foetus to the falling oxygen supply. In a previous paper (Rooth and Sjöstedt, 1957) on our investigations into 363 cases we were unable to confirm that there is any decrease in oxygen saturation with advancing pregnancy. And we are now unable to find any correlation between oxygen saturation in the cord vein and the amount of haemoglobin (Fig. 1). A low oxygen saturation observed after normal delivery seems to be of so short a duration that it does not influence the haemoglobin values.

There is also no correlation between oxygen saturation in the cord vein and haemoglobin values.

Summary

After normal deliveries the amount of haemoglobin and the oxygen saturation in the umbilical vein of newborn infants was determined. The mean haemoglobin level from the 40th to the 43rd week was 17·05 g. per 100 ml. During these four weeks there was no correlation between cord blood haemoglobin and the duration of pregnancy.

REFERENCES

DeMarsh, Q. B., Alt, H. L. and Windle, W. F. (1948). *Amer. J. Dis. Child.*, **75**, 860.

Dochain, J., Lemage, L. and Lambrechts, A. (1952). *Arch. franç. Pédiat.*, **9**, 274.

Drabkin, D. L. (1946). *J. biol. Chem.*, **164**, 703.

Kravkova, E. V. (1954). *Akus. i Ginek.*, no. 5, p. 16.

Marks, J., Gairdner, D. and Roscoe, J. D. (1955). *Archives of Disease in Childhood*, **30**, 117.

Mollison, P. L. (1951). *Blood Transfusion in Clinical Medicine.* Oxford.

Rooth, G. and Sjöstedt, S. (1957). *Acta obstet. gynec. scand.* In the press.

Vahlquist, B. (1941). *Acta paediat.* (*Uppsala*), **28**, Suppl. 5.

Walker, J. and Turnbull, E. P. N. (1953). *Lancet*, **2**, 312.

ATYPICAL CONGENITAL HAEMOLYTIC ANAEMIA

BY

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In recent years there has come to be recognized a group of haemolytic anaemias which are congenital and often familial, but in which the haematological findings are atypical. They cannot be classified with Cooley's anaemia or sickle cell anaemia or congenital spherocytosis. The group is heterogeneous and records of such cases are relatively few. Moreover the condition must be remembered in the differential diagnosis of neonatal jaundice. We therefore record the findings in two siblings one of whom presented as progressive pallor since birth, the other as neonatal jaundice.

Case Reports

Case 1. M.G. was referred to this hospital because of increasing pallor since birth. He was a first child, born of English parents on February 27, 1953. A great-grandfather is said to have been Spanish. The pregnancy had not been entirely normal, the mother having developed signs of mild toxaemia for which labour was induced prematurely. The delivery was otherwise normal and the baby appeared healthy (weight 6 lb. 13 oz.).

On admission he was a very pale but otherwise healthy looking infant, aged 10 weeks, and weighing 10 lb. The liver was palpable two and a half finger-breadths below the subcostal margin. The tip of the spleen could be felt at the level of the umbilicus. There were no other abnormal clinical signs. Radiographs of the entire skeleton revealed no abnormality. Haemoglobin was 32% (4·8 g. per 100 ml.), reticulocytes 14%, total leucocytes 18,000 per c.mm. (polymorphs 30%, lymphocytes 61%, monocytes 8%, eosinophils 1%). A stained film showed anisocytosis, polychromasia, nucleated red cells (30 per 100 leucocytes) and moderate numbers of target cells. Platelets appeared to be adequate. The serum bilirubin level was 0·9 mg. per 100 ml. A careful search for auto-antibodies in the infant's circulation yielded negative results. No incompatibility was found between the red cells of Mr. G. and the serum of Mrs. G. either in saline, or albumin, or after treatment with papain. Following a preliminary investigation of the bone marrow and erythrocyte osmotic fragility a blood transfusion was given. The subsequent course of the illness is shown in Fig. 1. Repeated transfusions were necessary to combat a rapidly developing anaemia, and ultimately, in Novem-

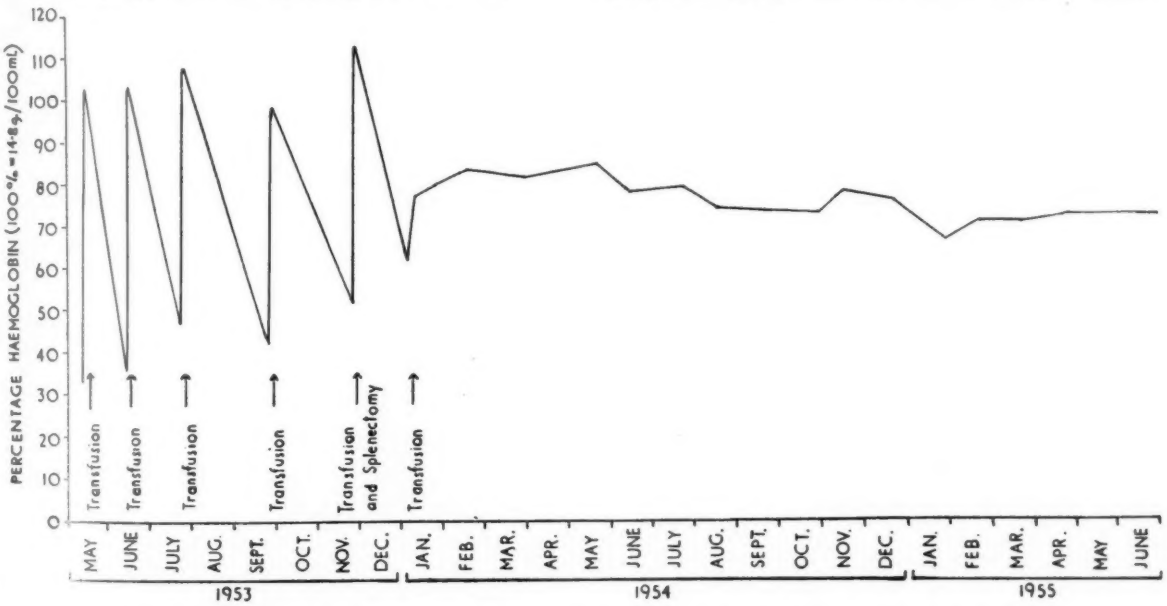

FIG. 1.—The chart shows the progress of the anaemia in the pre- and post-splenectomy periods in M.G.

ber, 1953, the spleen was removed by Mr. Nardell. One month earlier, on October 23, 1953, the case had been presented at the Royal Society of Medicine (Paediatrics Section) and both splenectomy and cortisone were suggested as possible lines of treatment. When therefore the haemoglobin continued to fall after removal of the spleen, it was decided to give cortisone a trial. The dosage used was 100 mg. daily for one month, 50 mg. daily for the second month, 25 mg. daily for the next two weeks, and finally 12½ mg. daily for two weeks. There was some recovery during this period, the haemoglobin reaching 85% where it remained for some time. Later it settled to between 70% and 75%, at which level it has remained without further transfusions.

Case 2. L.G., sister of M.G., was born on August 9, 1955, at the Mothers' Hospital, Clapton, under the care of Dr. Helen MacKay. A normal full-term pregnancy was followed by an uncomplicated delivery (birth weight, 6 lb. 6 oz.). Because it was known that the first child suffered from a form of haemolytic anaemia, the baby was closely observed and was noticed to be jaundiced four and a half hours after birth. Both liver and spleen were palpable. At 18 hours the haemoglobin was 108% (15·9 g. per 100 ml.), leucocytes 24,000 per c.mm. (polymorphs 66%, lymphocytes 26%, monocytes 7%, eosinophils 1%), platelets 400,000 per c.mm. A stained film showed anisocytosis and much polychromasia. No target cells were seen. A reticulocyte count was not made at this stage though it was obviously raised. Nucleated red cells numbered 10,500 per c.mm. No abnormal cells were seen. The serum bilirubin level was 10 mg. per 100 ml. Her general condition was satisfactory and no active measures were taken. Two weeks later the child was seen at Whipps Cross Hospital. She was pale and lethargic. The liver and spleen were palpable. Haemoglobin was 54% (7·9 g. per 100 ml.), reticulocytes 6·1%. A blood transfusion was given. One month later a second transfusion was necessary (Fig. 2) and it was decided to remove the spleen. This was done in October, 1955, by Mr. Nardell. After the operation the haemoglobin fell steadily, as in the case of the first child, but cortisone was withheld. On reaching 50% (7·4 g.) a vigorous spontaneous reticulocyte crisis occurred (24% on December 6) and was followed by a rise in the haemoglobin to 70%. It has remained at approximately this level ever since.

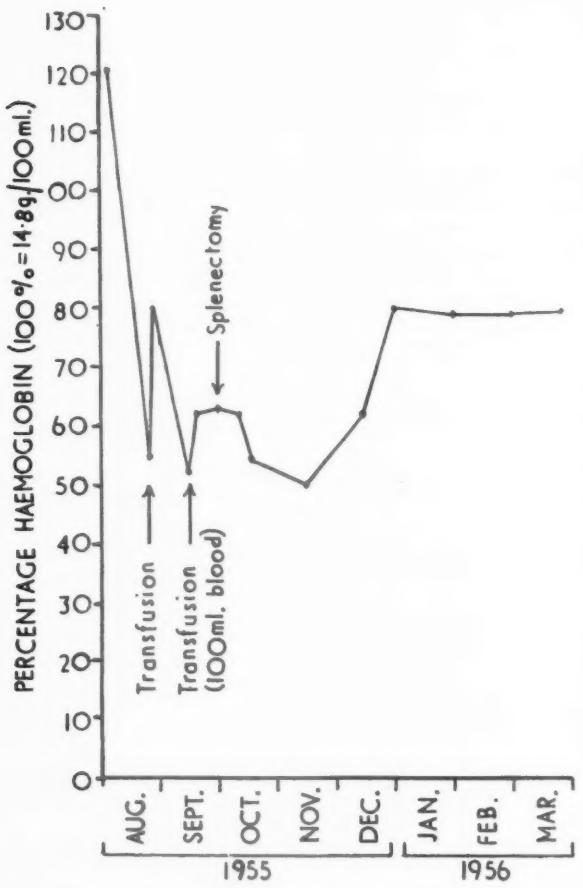

FIG. 2.—Progress of the anaemia in the case of L.G.♀. The recovery of the haemoglobin level after splenectomy and in the absence of cortisone therapy is clearly shown.

Recent radiographs of the skulls of both children appear normal.

Special Investigations

Bone Marrow. From M.G. a highly cellular marrow was obtained which showed an intense normoblastic response (L: E ratio = 0·54: 1). Leucopoiesis and platelet maturation were normal and no abnormal cells were seen. A single attempt to obtain a specimen from L.G. was unfortunately not very successful. Nucleated cells were scarce and no conclusion could be drawn.

M.C.D. Except for the first two weeks, the anaemia in both cases has been normocytic.

Osmotic Fragility. The method employed was that described by Dacie (1950). A stock phosphate-buffered solution is used, isotonic with 1% saline. Dilutions are made from this as required. Results are read colorimetrically.

In both infants repeatedly normal values were obtained both before and after incubation at 37° C. for 24 hours (Fig. 3). The fragility was not significantly altered by splenectomy in the case of M.G., while only post-splenectomy studies were made on the second child.

Autohaemolysis. Autohaemolysis was investigated according to the method of Selwyn and Dacie (1954) using defibrinated blood, and the effect of adding glucose to the specimen before incubation was observed. Estimations of haemolysis were made at 24 and 48 hours. Values obtained were within the upper limit of normal, and the presence of glucose was without apparent effect. This contrasted with the normal controls in which the presence of glucose inhibited haemolysis to a marked degree.

Faecal Urobilinogen. Faecal urobilinogen was estimated in the post-splenectomy period only. Values of

371 mg. (M.G.) and 399 mg. (L.G.) per 100 g. faeces were obtained.

Miscellaneous. Direct and indirect Coombs tests were negative. Sickling could not be induced. Electrophoresis failed to demonstrate any abnormal haemoglobins. The blood groups of the two infants and of eight near relatives are shown in Table 1.

Histology of Spleens. Dr. C. Raeburn reports:

'M.G. Greatly thickened splenic cords with increased cellularity. Sinuses relatively empty. Malpighian bodies well defined with Fleming centres in some and fairly numerous mitotic figures. Plentiful free iron present. Slight myeloid infiltration. Very little erythrophagocytosis.'

'L.G. The appearances are similar but less severe and there is much less free iron.'

Family Studies

Eight other members of the family were investigated.

TABLE 1
BLOOD GROUPS OF THE G. FAMILY

Name	ABO	Rh Phenotype	Probable Genotype	MN	S	P	Lu	Kell	Le^a	Le^b	F^a_y
M.G.	A		'Rh positive'								
L.G.	O	CcDee	CDe/cde	MN	+	+++	−	−	+	−	+
H.G.	A_1	CcDee	CDe/cde	MN	−	−	−	−	−	+	+
E.G.	A_1	CcDee	CDe/cde	MN	+	+++	−	−	−	+	+
J.B.	A_1	CcDee	CDe/cde	MN	−	+	−	−	−	−	−
V.S.	A_1		cde/cde	N	−	+++	−	−	−	+	−
A.G.	O	CcDee	CDe/cde	MN	−	+	−	−	−	+	+
B.G.	A_1		cde/cde	MN	−	−	−	−	−	−	+
F.R.	A_1	CcDee	CDe/cde	MN	+	+++	−	−	−	+	+
T.R.	O	CcDee	CDe/cde	MN	+	+++	−	−	−	+	+

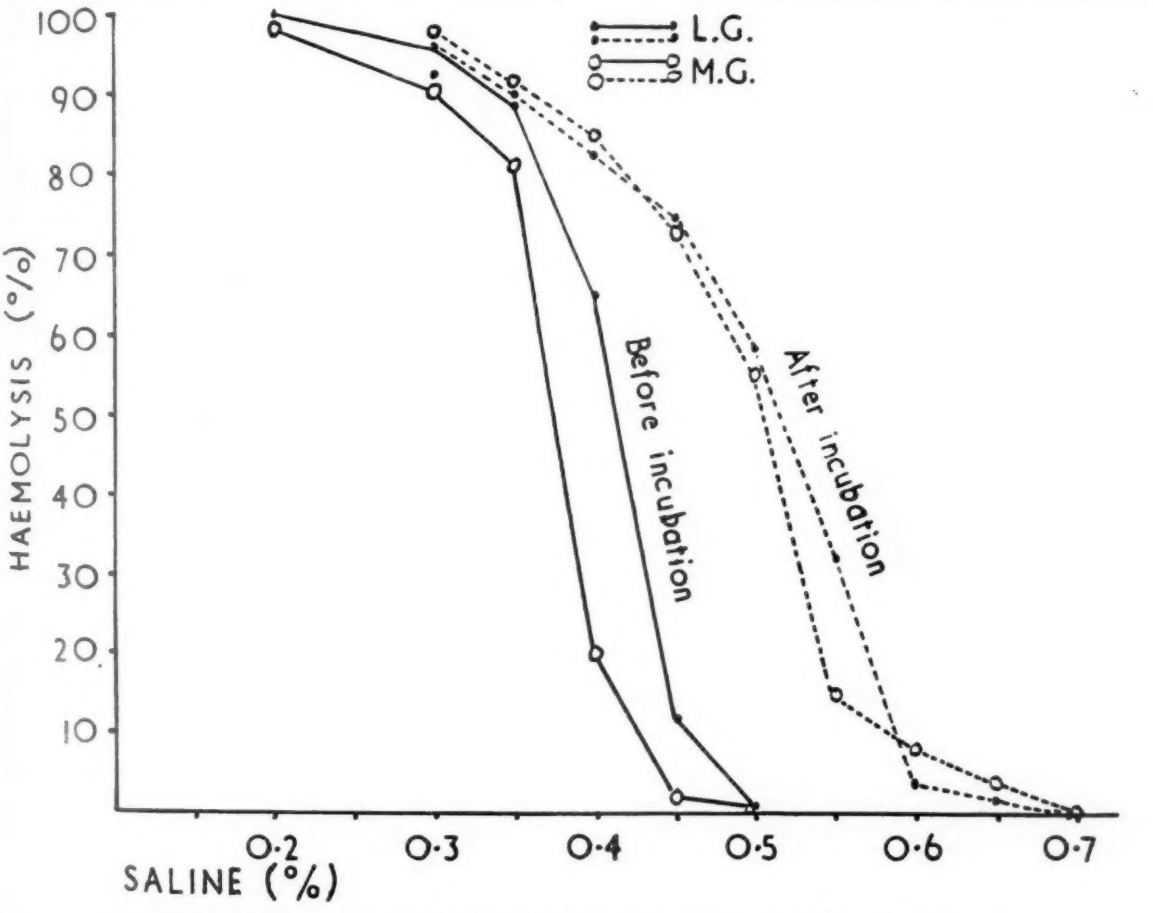

FIG. 3.—Osmotic fragility before and after incubation of the blood for 24 hours at 37° C in M.G. and L.G.

Their relationship is shown in Fig. 4. The following tests were carried out: Haemoglobin content, red cell and reticulocyte counts, examination of stained films of peripheral blood, Wassermann and Kahn tests, quantitative estimations of erythrocyte osmotic fragility both before and after incubation for 24 hours at 37° C., and all results were normal.

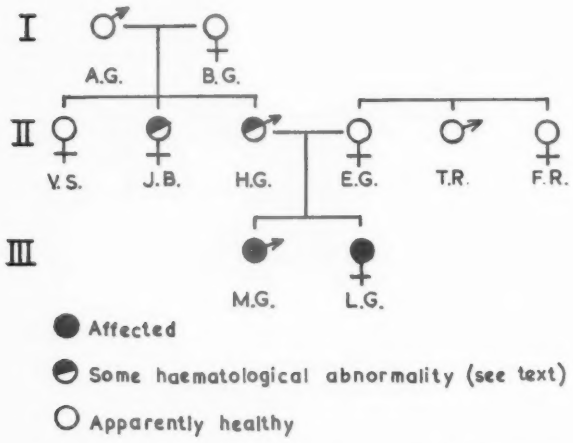

FIG. 4.—The G. family indicating the relationship of the persons listed in Table 1.

Studies of autohaemolysis also produced normal results except in one instance in which a paternal aunt (J.B.) showed 1·04% haemolysis at 48 hours which was unaffected by the presence of glucose. This finding was confirmed on a second occasion.

Estimations of serum bilirubin revealed normal values in all relatives except the father (H.G.). His family had noticed for many years that he was 'sometimes yellow', though he himself was unaware of any accompanying discomfort. His serum was unduly yellow to the naked eye and three estimations repeated at long intervals gave values between 1·2 and 1·5 mg. per 100 ml. Additional investigations in his case included electrophoresis of haemoglobin, total and differential serum proteins, a battery of liver function tests (alkaline phosphatase, thymol turbidity, cephaline cholesterol, zinc sulphate, Takata-Ara), and examination of urine for haemosiderin granules. All results were normal. A single estimation of faecal urobilinogen gave a result of 127 mg. per 100 g. faeces.

Discussion

The congenital haemolytic anaemias now comprise at least five distinct groups:

(*a*) Thalassemia (Cooley's anaemia) is characterized by a hypochromic anaemia which is refractory to iron, the presence of 'target' cells, a greatly decreased osmotic fragility and a pronounced racial incidence.

(*b*) Congenital spherocytosis (acholuric jaundice) in which microspherocytes are demonstrable in the peripheral blood, the osmotic fragility is increased, and the results of splenectomy are excellent.

(*c*) Hereditary elliptocytosis with haemolytic anaemia.

(*d*) The 'haemoglobinopathies' are almost confined to negroid races. The haemolytic anaemia may be of any grade of severity and is associated with the presence in the erythrocytes of an abnormal haemoglobin which is usually recognized by electrophoresis. The best known of this group is sickle cell anaemia.

(*e*) A miscellaneous group of atypical haemolytic anaemias.

It is with this last group that we are concerned. Thompson (1939) described a haemolytic anaemia in three families which exhibited certain unusual features. Erythrocyte morphology was normal and the cells could not be induced to sickle. Osmotic fragility was normal and splenectomy was valueless. Similar reports followed, the majority from America (Haden, 1947; Crosby, 1950; Kaplan and Zuelzer, 1950; Feinberg and Watson, 1951; Holliday, 1953; Lipton, Grossman and Richmond, 1953; Dacie, Mollison, Richardson, Selwyn and Shapiro, 1953; Motulsky, Crosby and Rappaport, 1954; Smiley, Dempsey, Villeneuve and Campbell, 1955), but it is clear that they are not all concerned with a single disease entity. For the purpose of classifying these anaemias certain common features are notable: (1) They are congenital and often familial. (2) Red cell morphology is normal and sickling cannot be induced. (3) Osmotic fragility of the erythrocytes is normal. (4) Splenectomy does not cure the disease. In addition basophilic stippling of the red cells has been conspicuous in some instances, and many of the anaemias have been macrocytic.

Not all these features are to be found together in any particular case, and their common factor is rather their exclusion from the other well defined categories. Dacie (1954) groups them together under the title 'Congenital Non-spherocytic Haemolytic Anaemias'. Selwyn and Dacie (1954) have divided their own cases into two types based on a major difference in behaviour on incubation of the patient's blood. Some of the methods they have used are complicated and are unlikely to become part of routine practice in the average hospital laboratory. The simplest of these measures is a study of autohaemolysis. By this means congenital spherocytosis can be differentiated from the non-spherocytic anaemias, and in addition a distinction may be made between the two types of the latter (Table 2).

In type I autohaemolysis is normal while in

TABLE 2

AUTOHAEMOLYSIS IN THE DIFFERENTIATION OF CONGENITAL HAEMOLYTIC ANAEMIAS (AFTER SELWYN AND DACIE)

	Autohaemolysis at 48 Hours	Effect of Added Glucose
Normal	0·4% to 3·5%	Marked inhibition—to less than 0·2%
Congenital spherocytosis	Greatly increased	Pronounced reduction of haemolysis but still above normal
Congenital non-spherocytic haemolytic anaemia Type I	Normal	No effect
Type II	Increased	No effect

type II it is increased. In neither case has the addition of glucose any appreciable effect on haemolysis.

The results of such tests applied to the cases described here suggest a close relationship with Selwyn and Dacie's type I. The haemolytic nature is borne out by the jaundice, the rapidly falling haemoglobin associated with a hyperplastic bone marrow and raised reticulocyte counts, and the increased excretion of faecal urobilinogen. Osmotic fragility is normal in both cases. No abnormal cells are present apart from the few target cells in the peripheral blood of M.G. Sickling cannot be induced. No abnormal haemoglobins are demonstrable. Autohaemolysis at 48 hours was within normal limits, and the addition of glucose to the blood was without effect.

The histology of the spleens conforms with the diagnosis of a non-spherocytic haemolytic anaemia. Motulsky *et al.* (1954) drew attention to the differences to be observed microscopically in the spleens from spherocytic and non-spherocytic haemolytic anaemias. They noted particularly the absence of congestion of the pulp cords in the latter and stated that

> '. . . a comparison of the splenic histologic findings in the two conditions suggests an explanation for the variation in response to splenectomy. The splenic pulp in hereditary spherocytosis is markedly congested with spherocytes . . . Removal of the spleen allows the spherocytes to live a normal life-span and the disease is cured. Failure to respond to splenectomy in hereditary non-spherocytic haemolytic disease may be related to the lack of congestion which can be explained by the normal shape of the affected red cells. No selective trapping occurs. After splenectomy the defective erythrocytes continue to be destroyed prematurely even in the absence of the spleen.'

In our cases splenectomy has not cured the disease but has apparently produced a worthwhile palliative effect. Neither child has required further transfusions and the haemoglobin level has been maintained, though at a sub-optimal level. The raised reticulocyte counts and the excessive excretion of faecal urobilinogen indicate the continuance of the haemolytic process. The two cases described by Kaplan and Zuelzer (1950) also received some benefit from splenectomy, but in contrast with those described in this paper, they both exhibited a raised osmotic fragility before operation. Such cases can expect some measure of relief when the spleen is removed. The cases of Lipton *et al.* (1953), however, showed a normal resistance to saline, yet were benefited by splenectomy.

Cortisone is not normally of any value in the management of congenital haemolytic anaemias and it is very doubtful whether it conferred any benefit when used on the elder child, since the younger improved spontaneously in exactly similar circumstances.

The question of inheritance in these cases is problematical. It is of interest that the only abnormal findings among members of the family, viz., the abnormal autohaemolysis in J.B. and the raised serum bilirubin in H.G., occur on the same side of the family tree, and it appears likely that the corpuscular defect manifest in the infants has been transmitted via the father. Dameshek and Singer (1941) have reported under the title 'Familial Haemolytic Jaundice: Constitutional Hepatic Dysfunction' instances of persistently raised serum bilirubin levels in families in which there was no evidence of haematological or hepatic dysfunction. H.G. presents just such a case, and it is probable that such patients are, in fact, instances of congenital non-spherocytic haemolytic anaemia.

Summary

Two cases of congenital haemolytic anaemia are recorded, the first presenting as increasing pallor since birth, the second as neonatal jaundice.

The clinical and haematological findings in both cases suggested haemolytic disease, though the nature of the haemolytic process was not at first evident.

The haematological observations upon which the final diagnosis is based are given in detail and particular attention is directed to the study of autohaemolysis as a means of differentiating congenital spherocytosis from the non-spherocytic haemolytic anaemias.

Splenectomy was beneficial to the extent of obviating the necessity for further blood transfusions though it did not halt the haemolytic process.

Family studies suggested that the defect was present in and transmitted by the father.

The diagnosis and modern classification of congenital haemolytic anaemias is discussed with special reference to the 'non-spherocytic group', recorded examples of which are still relatively few.

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References

Crosby, W. H. (1950). *Blood*, **5**, 233.
Dacie, J. V. (1950). *Practical Haematology*. London.
—— (1954). *The Haemolytic Anaemias*. London.
——, Mollison, P. L., Richardson, N., Selwyn, J. G. and Shapiro, L. (1953). *Quart. J. Med.*, **22**, 79.
Dameshek, W. and Singer, K. (1941). *Arch. intern. Med.*, **67**, 259.
Feinberg, A. W. and Watson, J. (1951). *Blood*, **6**, 357.
Haden, R. L. (1947). *Amer. J. med. Sci.*, **214**, 255.
Holliday, T. D. S. (1953). *J. clin. Path.*, **6**, 219.
Kaplan, E. and Zuelzer, W. W. (1950). *Blood*, **5**, 811.
Lipton, E. L., Grossman, H. J. and Richmond, J. B. (1953). *Pediatrics*, **12**, 384.
Motulsky, A. G., Crosby, W. H. and Rappaport, H. (1954). *Blood*, **9**, 749.
Selwyn, J. G. and Dacie, J. V. (1954). *Ibid.*, **9**, 414.
Smiley, R. K., Dempsey, H., Villeneuve, P. and Campbell, J. S. (1956). *Ibid.*, **11**, 324.
Thompson, W. P. (1939). *Bull. N.Y. Acad. Med.*, **15**, 177.

THE NATURAL HISTORY OF NEPHROSIS

BY

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The suffix 'osis' signifies 'a diseased condition' and hence nephrosis means a diseased condition of the kidney (Webster's New International Dictionary). The term nephrosis was used by Müller (1905) to differentiate what he considered degenerative renal disease from other renal conditions to which the term nephritis was applied. He pointed out that hitherto the word nephrosis had been used to describe disorders of the renal pelvis (hydronephrosis, pyonephrosis), but considered that it would be more appropriate to use it for certain diseases of the kidney itself. Volhard and Fahr (1914) classified renal diseases into three groups: (1) Nephroses, in which degenerative lesions were present, with or without amyloidosis; (2) nephritides or inflammatory lesions; and (3) scleroses or arteriosclerotic diseases. Munk (1925) considered that the term nephrosis should be used for all degenerative renal lesions whether of albuminous, fatty, lipoid, necrotic, hyaline, amyloid or glycogen types. Evans (1932) restricted the term nephrosis to those types of Bright's disease which were associated with syphilis or amyloidosis. Allen (1952) used the term nephrosis for either chronic glomerular diseases of the kidney with oedema (lipoid nephrosis) or tubular diseases involving the proximal, distal or both parts of the renal tubules. Fishberg's (1954) conception of nephrosis is of a non-inflammatory disease of the nephron including necrotizing nephrosis, chronic lipoid nephrosis, diabetic glomerulosclerosis (the Kimmelstiel-Wilson syndrome), amyloidosis and toxaemia of pregnancy. By virtue of long usage the term 'pure' nephrosis has been applied to degenerative conditions of the renal tubules caused either by poisons, for example, mercury, lead, arsenic, or by general diseases, for example, syphilis and amyloidosis.

These concepts of nephrosis are based largely upon histological evidence of damage to different parts of the nephron, but to many other writers nephrosis is a clinical rather than a histological entity, a view which has been well summarized by Kramer, Goldman and Cason (1952) in the following terms:

> 'Nephrosis occupies a position shared by few diseases in medicine; its aetiology is unknown, its course unpredictable, its prognosis uncertain and its treatment unsatisfactory. Nevertheless, its cardinal manifestations—oedema, hypoproteinaemia, albuminuria, hypercholesterolaemia—are so striking, and the remissions and exacerbations at times so dramatic as to challenge the attention of both the clinician and the scientist.'

Ellis (1942) attempted to correlate the clinical features and the histological changes encountered in Bright's disease. His researches, carried out over a 20-year period at the London Hospital and based upon 370 patients, resulted in the concept of two types of nephritis with dissimilar clinical and histological features. In type 1 Ellis nephritis the illness is of sudden onset, is often preceded by an acute streptococcal throat infection, has haematuria as the most prominent feature and is followed by complete recovery after about six weeks in over 80% of the patients. Type 2 Ellis nephritis is of insidious onset, is without preceding throat infection, has oedema as the most marked feature and carries a poor prognosis. Confirmation of the views expressed by Ellis has come from many workers including Davson and Platt (1949) who also stated that 'the concept so common in textbooks of oedematous nephritis as a usual intermediate stage between acute and chronic phases is at variance with clinical experience'.

It could be argued that the use of the term nephrosis has confused rather than clarified our knowledge of Bright's disease and to some extent this is true. I would suggest that nephrosis be no longer used when the cause of the renal disturbance is known, as, for example, in amyloid disease, syphilis, mercury poisoning, but that the more appropriate terms such as 'renal amyloidosis' or 'renal syphilitic disease' or 'mercurial tubular degeneration' should be employed. It would seem reasonable to retain the term nephrosis, which is a

conveniently short word without aetiological connotation, to describe the condition of those patients who have no evidence of amyloidosis, syphilis, diabetic nephrosclerosis, renal vein thrombosis, but who present many of the following features: An illness of insidious onset with the main clinical findings of generalized oedema and pallor; no history of recent throat infection; marked albuminuria, with little or no haematuria; normal blood pressure; lowered plasma protein levels, raised blood cholesterol and normal blood urea concentrations; a prolonged course lasting many months or years.

The use of the word nephritis with division into types 1 and 2 implies that these two conditions are intimately related, whereas the symptoms and signs, the biochemical abnormalities in the blood, treatment, prognosis and histological appearance of the kidneys are so obviously dissimilar.

In medical paediatric practice three main clinical types of renal disease are commonly met: (*a*) a condition of sudden onset, with haematuria as the most obvious feature, sometimes called type 1 Ellis nephritis but for which I would prefer the descriptive term 'acute (haemorrhagic) nephritis'; (*b*) an illness having the six main features described above, sometimes called type 2 Ellis nephritis but which I would call 'nephrosis'; and (*c*) a form of renal disease with increasing evidence of renal insufficiency resulting either from acute nephritis or from nephrosis or following recurrent attacks of pyelonephritis or occurring in association with a congenital renal lesion, which I would call 'chronic nephritis'. The patients reported in this paper were suffering from nephrosis as I have defined it above, and were admitted to Alder Hey Children's Hospital, Liverpool, during the eight-year period 1948 to 1955 inclusive. They were all seen personally during some stage of the illness and have been followed up either in the Out-patient Department or when readmitted to the wards.

Thirty-two patients have been observed, 21 being males and 11 females. The age of onset of the illness is shown in Fig. 1, from which it is apparent that 11 (34%) of the patients were under 3 years of age, 14 (44%) between 4 and 7 years, and 7 (22%) over 7 years of age when first seen. A survey of the literature shows that during this eight-year period six large series of patients with nephrosis were reported, and of a total of 349 patients, 228 (65%) were under 3 years of age, 71 (20%) between 4 and 7 years and 50 (15%) over 7 years of age.

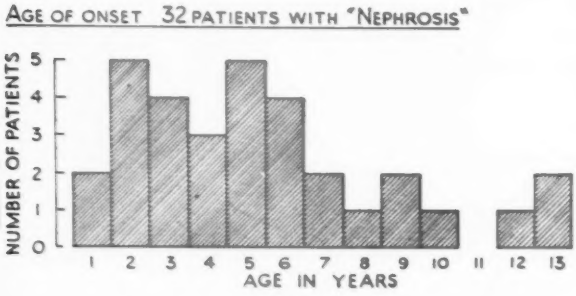

FIG. 1.

Mode of Onset

The mode of onset was insidious in all patients and there was a period of general ill health varying from a few weeks to several months before the onset of oedema. In a few patients increasing abdominal girth had been noticed. The onset was closely related to the first immunizing injection against diphtheria in one infant aged 7 months, and in another child it was related to the 'booster' diphtheria injection when he was 5½ years old. I do not know the significance of these observations but it is possible that the onset of the disease in close association with diphtheria immunization was entirely fortuitous. There was no family history of allergic disorders or nephritis in any of the patients.

Clinically the degree of oedema was variable but many patients showed gross generalized oedema when first admitted to hospital. The urine in all patients was loaded with albumin; in a few patients red blood cells were found on microscopical examination, and macroscopic blood was present in two patients for a short period.

Biochemical Investigations

Biochemical investigations showed that the level of blood urea was below 40 mg. % in 28 of the 32 patients and in the remaining four it showed a temporary elevation. The serum cholesterol values were raised to an average of 470 mg. %. The serum protein levels on admission averaged 4·2 g. % and the albumin fraction was especially reduced; this led to an alteration of the albumin/globulin ratio from the average normal of 1·25 to 1 to a figure as low as 0·05 to 1, at which point albumin comprises as little as 5% of the total protein. The electrophoretic pattern of the globulin fraction was studied in six of the patients, and at the time of their admission to hospital the most striking features were a diminution of the γ globulin and an increase in α_2 globulin. When the electrophoretic pattern is studied in relation to the clinical response of the patient it is apparent that disappearance of oedema and gross albuminuria may precede by many weeks a return to biochemical normality. For example, in one patient the total protein level rose from

4 g. % to 6·1 g. % over a period of one month, but at this stage the albumin/globulin ratio was still abnormal. During the following six weeks this ratio returned to normal (1·21 to 1). The level of γ globulin showed a steady rise but even after nearly three months had not returned to normal; α_2 globulin was raised initially (1·43 g. %) and after nearly three months had fallen to a normal level (0·84 g. %).

Course of the Disease

The course of the disease could not be predicted on the basis of the history, the clinical features on admission or on the results of the initial biochemical investigations. The duration of the illness varied from three months to five and a half years in patients who eventually recovered and from six weeks to seven and a half years in those who died (Fig. 2). In many patients the course of the illness was characterized by remissions and exacerbations, and in some instances these variations were related to the development of infections (Table 1). In general terms, acute upper respiratory tract infections were associated with increase in oedema, whereas pneumococcal peritonitis and measles were followed by lessening or disappearance of oedema. In one child there was a complete remission (clinical and biochemical) following measles and this remission lasted for over two years. Barness, Moll and Janeway (1950), reporting upon 161 patients who developed 298 infective episodes, found that infections provoked remissions in 25% of cases, exacerbations in 49% and no change in 26%.

TABLE 1
THE EFFECT OF INFECTIONS UPON OEDEMA

Type of Infection	More Oedematous	No Change	Less Oedematous
U.R.T. infection	4	3	1
Streptococcal throat ..	2	1	3
Bronchitis	0	1	0
Measles	0	1	3
Whooping cough	0	1	0
Pneumococcal peritonitis	1	1	3
Dysentery	1	2	1
Malaria	0	1	0
Total ..	8	11	11

Treatment

The many therapeutic measures which have been recommended for patients with nephrosis are eloquent enough testimony to the unsatisfactory nature of the therapy prescribed. Reports advocating a particular form of treatment are published from time to time, but the good results claimed are not easily obtained by other clinicians. The main forms of therapy (Table 2) are designed either to increase

TABLE 2
CHIEF THERAPEUTIC MEASURES USED IN NEPHROSIS

1. Increase plasma proteins
   (*a*) High-protein diet
   (*b*) Intravenous plasma
2. Control oedema
   (*a*) Mechanical—paracentesis (abdominis or thoracis)
   (*b*) Raise colloid osmotic pressure—gum acacia, 'dextran'
   (*c*) Lower extracellular sodium and chloride levels
   —restrict salt intake
   —ion exchange resins
   (*d*) Renal—mersalyl
   —urea
3. Control infections—preventive (streptococci)
   —curative (pneumococci)
4. By specific infections—measles
   —malaria
5. By hormones—thyroid
   —adrenocorticotrophin
   —cortisone : prednisolone
6. Morale of parents and patient

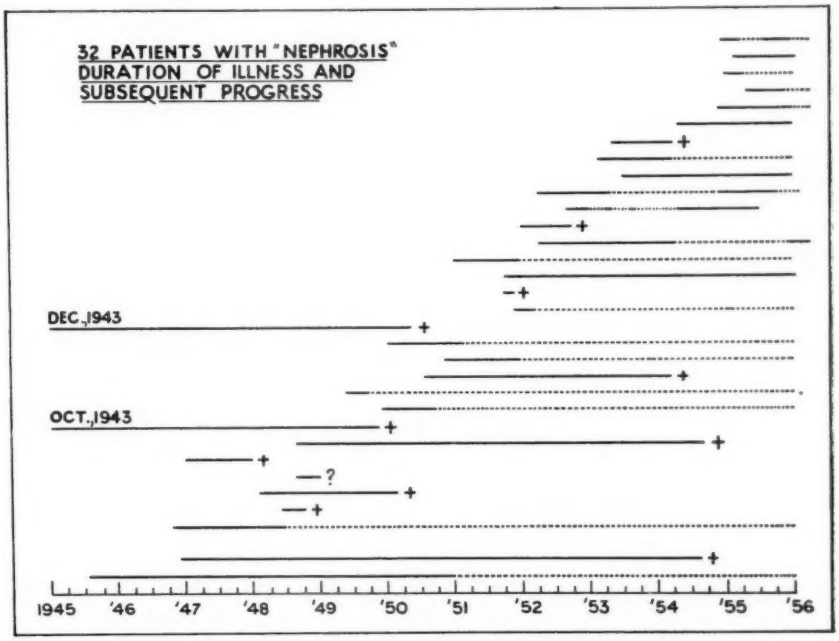

FIG. 2.—Duration of illness of 32 patients with 'nephrosis'.
Continuous line = disease active. Interrupted line = no evidence of activity.

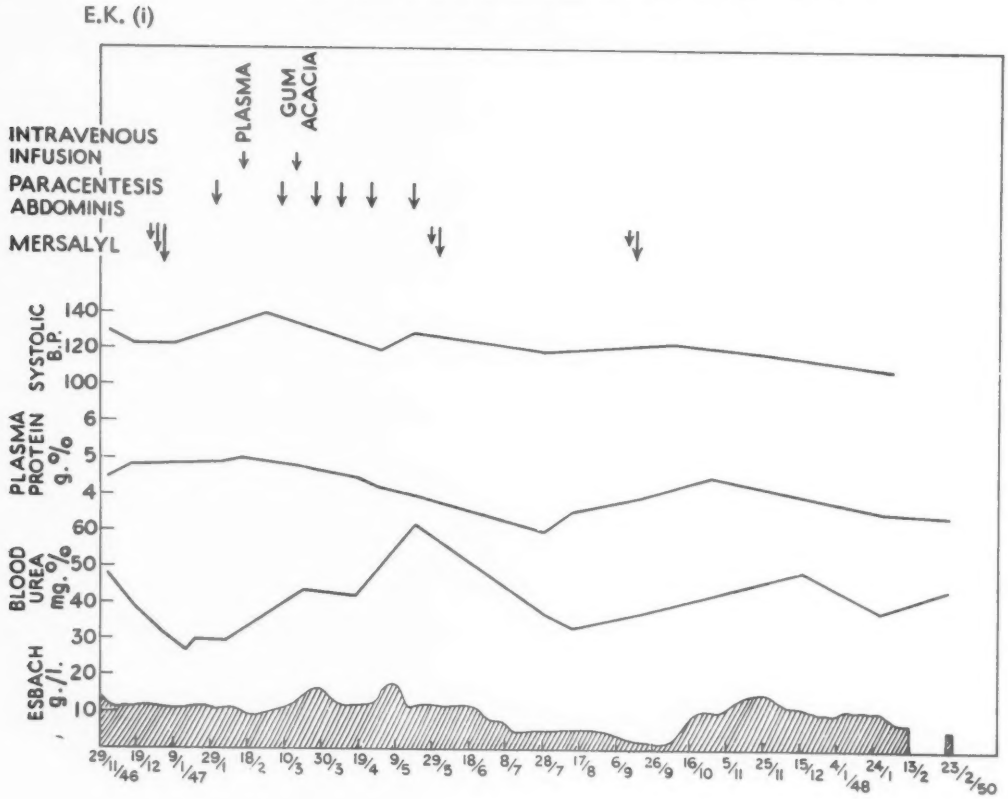
E.K. (i)
INTRAVENOUS INFUSION
PLASMA
GUM ACACIA
PARACENTESIS ABDOMINIS
MERSALYL
SYSTOLIC B.P.
PLASMA PROTEIN g.%
BLOOD UREA mg.%
ESBACH g./l.
29/11/46 19/12 9/1/47 29/1 18/2 10/3 30/3 19/4 9/5 29/5 18/6 8/7 28/7 17/8 6/9 26/9 16/10 5/11 25/11 15/12 4/1/48 24/1 13/2 23/2/50

FIG. 3.

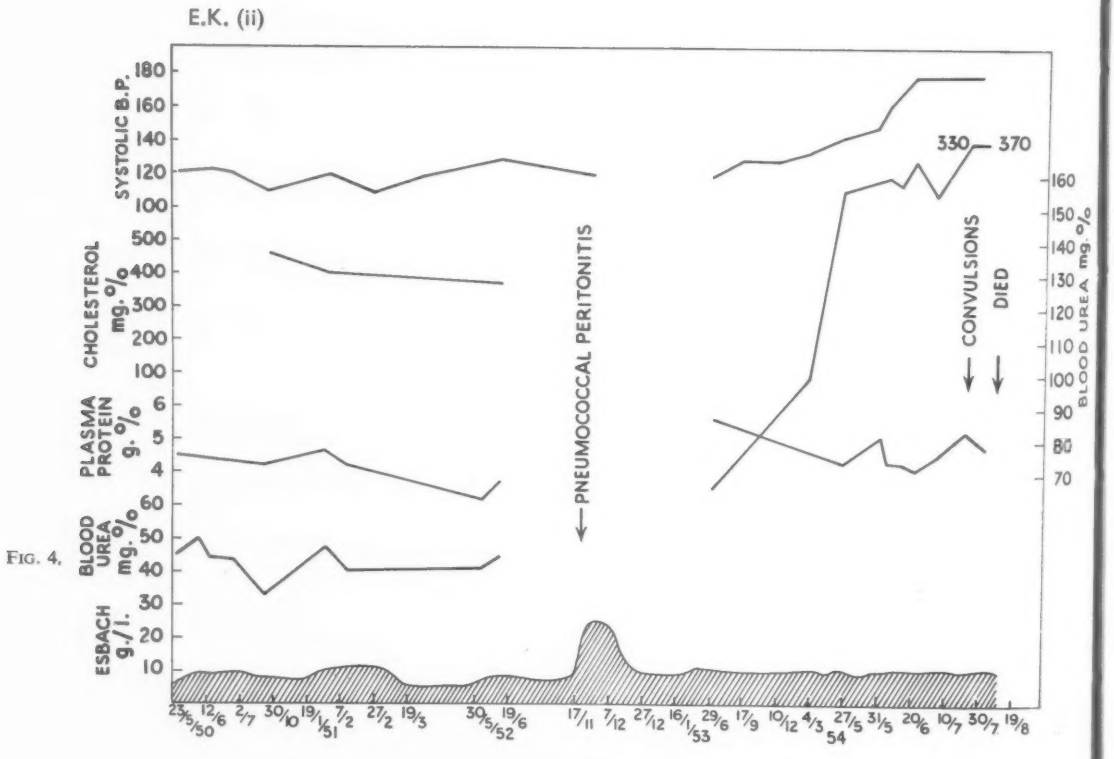
E.K. (ii)
SYSTOLIC B.P.
CHOLESTEROL mg.%
PLASMA PROTEIN g.%
BLOOD UREA mg.%
ESBACH g./l.
PNEUMOCOCCAL PERITONITIS
330 370
CONVULSIONS
DIED
23/5/50 12/6 2/7 30/10 19/1/51 7/2 27/2 19/3 30/5/52 19/6 17/11 7/12 27/12 16/1/53 29/6 17/9 10/12 4/3/54 27/5 31/5 20/6 10/7 30/7 19/8

FIG. 4.

the level of plasma proteins, or to decrease the marked oedema so characteristic of nephrosis, or to control the infections which these patients are so prone to develop. The 32 patients reported here all received a high-protein, low-salt diet, and in addition one or more of the remedies listed in Table 2.

One patient (E.K.), who was seen over an eight-year period, received many of the forms of therapy available before hormones were used (Figs. 3 and 4). He received a high-protein diet with restriction of sodium intake during the entire eight years, intravenous infusions of plasma and gum acacia, numerous abdominal paracenteses, and mersalyl injections. He developed pneumococcal peritonitis which responded satisfactorily to penicillin therapy after which he lost all the oedema, and he finally died in uraemia after an episode of pericarditis. Unfortunately post-mortem examination was refused so that the macroscopical and microscopical features of the kidneys were not revealed.

The effect of corticotrophin (A.C.T.H.) and cortisone on the natural history of nephrosis has been observed by many workers. In 1951 Luetscher, Deming and Johnson reported the elimination of oedema in 14 patients after treatment with A.C.T.H.; Riley (1952) claimed remissions in 50 patients treated with A.C.T.H. or cortisone; Heymann, Gilkey and Salehar (1955) gave repeated short courses of A.C.T.H. or cortisone lasting 10 to 12 days to 64 children and diuresis occurred in 1,952. The average duration of remissions was 4·2 months after A.C.T.H. and 2·6 months after cortisone. Lange, Slobody and Strang (1955) reported clinical remissions after A.C.T.H. and cortisone but stated that they were short-lived and that recurrences were frequent. Arneil and Wilson (1952, 1953) confirmed the diuretic effect of A.C.T.H. and cortisone but considered that these hormones were of limited value. Four patients in my series of 32 patients were given A.C.T.H. and 13 received cortisone; nine of these 13 patients became less oedematous either during hormone therapy or after it had been discontinued abruptly (Table 3). This response

TABLE 3
EFFECT OF A.C.T.H., CORTISONE AND PREDNISOLONE ON OEDEMA

	No Effect	More Oedematous	More Oedematous and Diuresis when Stopped	Less Oedematous
A.C.T.H. (4) ..	1	1	1	1
Cortisone (9) ..	2	2	2	3
Prednisolone (4) ..	—	—	—	4

may be, in part, the result of changes in blood electrolyte concentrations especially involving sodium, but two synthetic cortisone compounds (prednisone and prednisolone) are now available which do not have the marked sodium-retaining activity nor do they provoke the same degree of hypertension as do cortisone or A.C.T.H.

It has been our practice to prescribe a total of 45 mg. of prednisolone in divided doses three times daily until the patient is clinically free from oedema. The dose is then reduced by 5 mg. every third or fourth day until a maintenance dose of 5 to 10 mg.

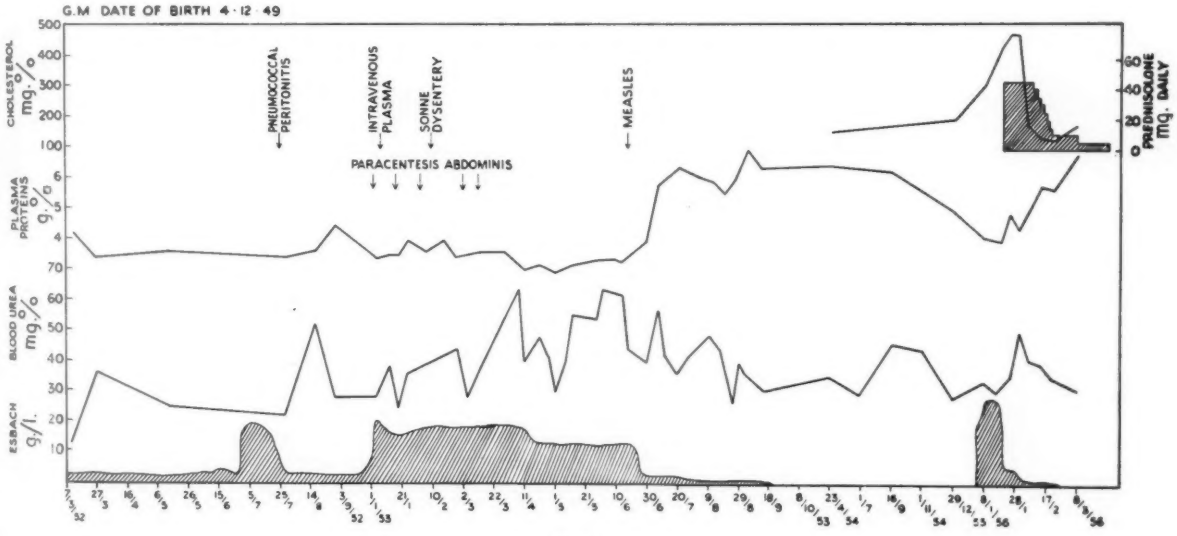

FIG 5.

is reached. This dose is continued until the biochemical changes, including the protein electrophoretic pattern, have returned to normal.

Fig. 5 illustrates the course of nephrosis in a patient who had a remission which lasted for over two years following measles; after this period he relapsed but marked clinical and biochemical improvement followed therapy with prednisolone.

Results of Therapy

The fate of these 32 patients is recorded in Table 4 which shows that a third of the patients died, that nearly a third can be considered 'cured' and that a further 15% are probably cured, although the short follow-up period precludes a definite opinion.

TABLE 4
FATE OF 32 PATIENTS WITH 'NEPHROSIS'

'Cured'	
long-term (at least 1 year)	9
short-term (under 1 year)	5
Still active	6
Died	11
Unknown	1

In Ellis's original paper the recovery rate in 145 patients was about 5%. A survey of the recent literature suggests that this figure provides too pessimistic a view. In a series of 208 patients published by Barness *et al.* (1950) 50% of the patients showed complete recovery when seen two to 23 years after the initial illness. Schwartz, Kohn and Weiner (1943) studied 40 patients for periods up to 20 years and report that 45% recovered completely. Farr (1943), studying 36 patients reported a recovery rate of 28%, whereas Greenman, Weigand and Danowski (1955) reported that 22 out of 30 patients (73%) were entirely normal, but the follow-up period extended only for two years. Rapoport, McCrory and Sohn (1955) studied 40 patients during the years 1949-52 and 44% of these had a complete remission, whereas in a further 30 patients studied in 1953 and 1954 complete remissions were reported in 67% but again in this latter group the follow-up period was only one year.

It appears from these published reports that about 50% of patients recover completely from this disease. Complete recovery implies absence of oedema and albuminuria and a normal blood chemistry. There are, however, other patients who are symptomless and in whom the blood chemistry is normal, but in whom a trace of urinary albumin persists for many months or years.

Post-mortem Appearances

Eleven of the patients in my series died and post-mortem examination was permitted in seven of them. The macroscopical and microscopical features were of two main types: (*a*) three patients showed the changes associated with chronic nephritis, and (*b*) four patients showed the classical features described by Ellis for type 2 nephritis.

(*a*) These three patients were aged 4½ years, 8½ years and 12 years when the first symptoms and signs of illness were apparent, and the illness continued for seven, six and five years respectively. During the last eight to 12 months of life there was evidence of renal insufficiency, with cardiac hypertrophy, increasing hypertension, and markedly raised blood urea level. One child also developed exudates and haemorrhages in the optic fundi. The post-mortem findings were very similar in the three patients; the kidneys were small, contracted and granular, the cortex was ill-defined and the capsule was adherent; microscopically the glomeruli were few and replaced by fibrous tissue, and many of the tubules were dilated.

(*b*) These four patients developed clinical evidence of nephrosis when aged 1½, 3, 5½ and 12 years old and the duration of the illness was 14 weeks, 12 months, 16 weeks and eight months for the respective patients. None of them showed signs of uraemia, the blood pressure remained within the limits of normal and the blood urea level did not rise above 60 mg. %. Three of the four children had fluid in the pleural and peritoneal cavities from which pneumococci were grown. The kidneys were larger than normal and pale, with well marked differentiation of cortex and medulla. Histologically there was dilatation of the tubules, an increase in the interstitial tissue, tufting of the glomeruli and hyalinization of the basement membrane of the glomeruli.

Summary

The word 'nephrosis' has been used to describe a variety of renal disorders but in this paper its use is limited to a well defined clinical condition of unknown aetiology, the chief features of which are generalized oedema, heavy albuminuria and lowered plasma proteins.

Thirty-two children with nephrosis have been observed at Alder Hey Children's Hospital, Liverpool, during the eight-year period 1948 to 1955, and the natural history of the disorder has been studied.

The electrophoretic pattern of plasma proteins has been investigated and characteristic changes in γ and α_2 globulin levels are described. Clinical recovery may precede biochemical recovery and treatment should therefore be continued until the electrophoretic pattern of proteins is normal.

The response to well-established therapeutic measures was disappointing but response of some

of the patients to hormone therapy and especially to prednisolone has been most encouraging.

Eleven of the 32 patients died, nine can be considered 'cured' and a further five show no clinical abnormalities but the follow-up period is too short to evaluate prognosis.

The post-mortem findings in seven patients are described and were of two main types depending upon the duration of the illness. Four patients with an illness lasting a few months showed the changes described by Ellis for type 2 nephritis, and three patients with an illness lasting several years showed the changes associated with chronic nephritis.

References

Allen, A. C. (1952). *The Kidney*. London.

Arneil, G. C. and Wilson, H. E. C. (1952). *Archives of Disease in Childhood*, **27**, 322.

—, —— (1953). *Ibid.*, **28**, 372.

Barness, L. A., Moll, G. H. and Janeway, C. A. (1950). *Pediatrics*, **5**, 486.

Davson, J. and Platt, R. (1949). *Quart. J. Med.*, **18**, 149.

Ellis, A. (1942). *Lancet*, **1**, 1.

Evans, G. (1932). In Ball, W. G. and Evans, G., *Diseases of the Kidney*. London.

Farr, L. E. (1943). *Amer. J. Dis. Child.*, **65**, 362.

Fishberg, A. M. (1954). *Hypertension and Nephritis*, 5th ed. Philadelphia.

Greenman L., Weigand, F. A. and Danowski, T. S. (1955). *Amer. J. Dis. Child.*, **89**, 169.

Heymann, W., Gilkey, C. and Salehar, M. (1955). *Pediatrics*, **15**, 49.

Kramer, B., Goldman, H. and Cason, L. (1952). *J. Pediat.*, **41**, 792.

Lange, K., Slobody, L. and Strang, R. (1955). *Pediatrics*, **15**, 156.

Luetscher, J. A., Deming, Q. B. and Johnson, B. B. (1951). *J. clin. Invest.*, **30**, 1530.

Müller, F. (1905). *Verhandlungen der deutschen Pathologischen Gesellschaft Meran*, pp. 64-99.

Munk, F. (1925). *Pathologie und Klinik der Nierenerkrankungen*, pp. 185-364. Berlin.

Rapoport, M., McCrory, W. and Sohn, W. (1955). *Amer. J. Dis. Child.*, **90**, 631.

Riley, C. M. (1952). *J. Amer. med. Ass.*, **150**, 1288.

Schwarz, H., Kohn, J. L. and Weiner, S. B. (1943). *Amer. J. Dis. Child.*, **65**, 355.

Volhard, F. and Fahr, T. (1914). *Die Brightsche Nierenkrankheit*. Berlin.

MALIGNANT HYPERTENSION IN A CHILD DUE TO UNILATERAL KIDNEY DISEASE

BY

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Unilateral malignant nephrosclerosis appears to be a rare condition. In a review of the literature Manners (1954) was only able to find reports of two cases in children and five cases in adults. This author also reported a further case in a child of 3 years, in whom the most significant finding at necropsy was partial obstruction of the left renal artery at its origin due to swelling of the aortic intima. Whereas on microscopy the left kidney appeared completely normal, the right kidney showed severe malignant nephrosclerosis. The pathogenesis of the aortic intimal swelling was not clear, but the possibility that it represented an organized thrombus was considered.

The rarity of the syndrome prompts us to publish a case from our hospital bearing a close resemblance to that of Manners.

Case Report

T.T., an 8-year-old African girl, was admitted to hospital on July 1, 1955, with a seven months' history of blurred vision and headaches, and a three years' history of attacks of abdominal pain associated with vomiting occurring at one to two monthly intervals. She had suffered from measles, whooping cough, and ascariasis at an early age, but there was no history of sore throat, haematuria, oedema, dyspnoea or weight loss. Her appetite had been poor for some time.

On admission she was dull and lethargic but appeared to be comfortable in the recumbent position. She was apyrexial, her weight was 42 lb., and though of slight build, there was no evidence of nutritional, skin or hair changes, and there was no oedema or hepatomegaly.

The heart was enlarged, the apex impulse heaving in character, and a triple rhythm was present. The rate was 100 and the blood pressure 235/185 mm. Hg in the right arm, and in both legs was 260/220 mm. Hg. The femoral pulses were easily palpable and there was no evidence of cardiac failure. Electrocardiography confirmed a gross left ventricular hypertrophy.

The fundi showed a severe grade IV retinitis with haemorrhages, typical macular stars and widespread macular oedema. A catheter specimen of urine contained a heavy deposit of protein, the specific gravity was 1022 and microscopic examination revealed hyaline casts, epithelial cells, occasional red cells and 2 to 3 polymorphonuclears per high-power field. The blood urea was 43 mg./100 ml., the haemoglobin 14·7 g.% with a normal leucocyte count. The serum sodium was 118 mEq./litre, the serum potassium 4·1 mEq./litre and the plasma chlorides 102 mEq./litre.

Intravenous pelography showed a large but apparently normal right kidney and pelvis, and a poorly functioning left kidney which showed up faintly 60 minutes after injection of the dye (Fig. 1). A retrograde pyelogram was attempted but catheterization of the left ureter was unsuccessful. The bladder was normal. Tests for

FIG. 1.—Intravenous pyelogram showing a poorly functioning left kidney.

phaeochromocytoma were negative and in view of persistent severe hypertension and apparent deficient left kidney function it was considered advisable to remove the left kidney.

The child was given a slow intravenous infusion of 5% dextrose before operation to facilitate control and the administration of medicaments during anaesthesia.

At operation, eight days after admission, the left kidney was found to be small, hard, compressed against the vertebral column and lying almost transversely. No aberrant renal vessel or ureteric anomaly was present, and there was no evidence of any inflammatory process. The suprarenal gland was normal. A left nephrectomy was performed. The pathological report on the removed kidney was as follows:

The kidney (30 g.) was smaller than normal. The capsule stripped with slight difficulty leaving a finely granular surface. In addition there were a few deeper cortical scars. On section there was no alteration in the cortico-medullary ratio, but there was slight congestion of the cortex and medulla. Microscopically, an occasional glomerulus showed complete hyalinization while others showed partial fibrosis with intracapsular adhesions. These changes were focal. The vessels and tubules appeared normal. There were foci of interstitial lymphocytic and histiocytic infiltration, especially around the glomeruli and small vessels in the subcapsular region. No abnormality was observed in the pelvis (Figs. 2 and 3).

Immediately after nephrectomy the blood pressure dropped to 140/120 mm. Hg. Post-operatively the child was given 500 ml. 0·9% sodium chloride in 5% dextrose followed by 500 ml. 5% dextrose. The day after operation the serum sodium level was 128 mEq./litre, the serum potassium level 5·0 mEq. and the blood urea level had risen to 121 mg./100 ml. She had passed no urine up till 24 hours after operation and catheterization produced 3½ oz. of dark bloody fluid. No bowel movement had taken place, but there was no vomiting or distension. The blood pressure at this time was 150/110 mm. Hg.

Forty-eight hours after operation she vomited, and in the course of the next two days the blood urea level rose to 190 mg./100 ml., the serum potassium to 5·9 mEq. and the serum sodium dropped to 109 mEq./litre. A few watery stools were passed. She was given a further intravenous infusion of 0·45% sodium chloride in 5% dextrose. The blood pressure rose to 180/120 mm. Hg and she continued to pass watery stools and a very small quantity of urine each day.

On the ninth post-operative day the condition wor-

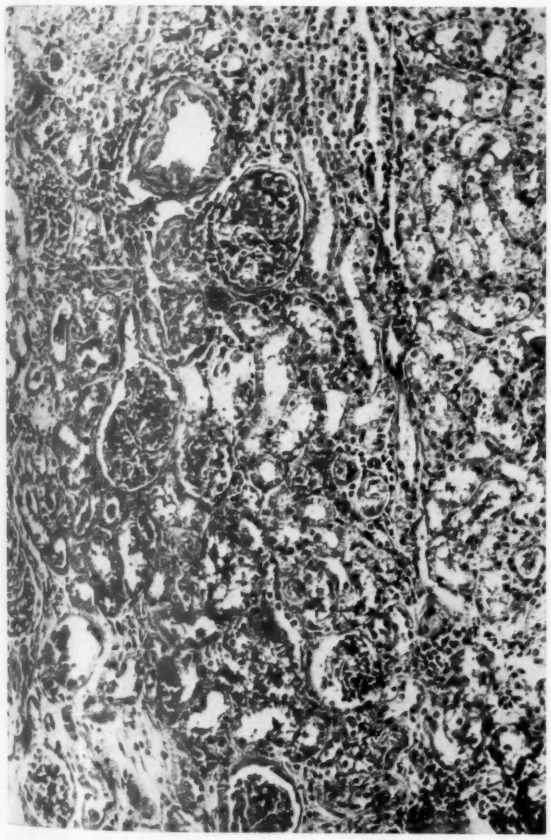

FIG. 2.—Section of the left kidney showing complete absence of any nephrosclerotic changes. Haematoxylin and eosin × 100.

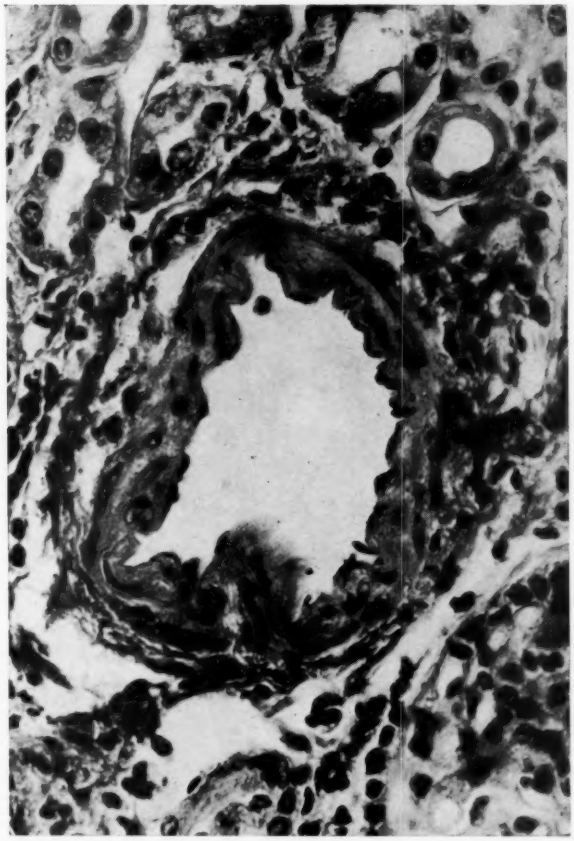

FIG. 3.—High-power view of one of the smaller arteries seen in Fig. 2. Haematoxylin and eosin × 400.

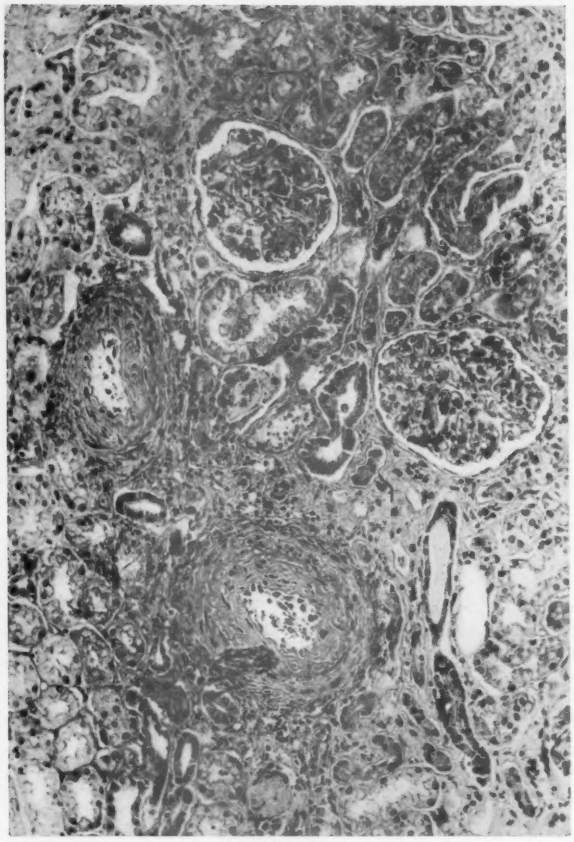

FIG. 4.

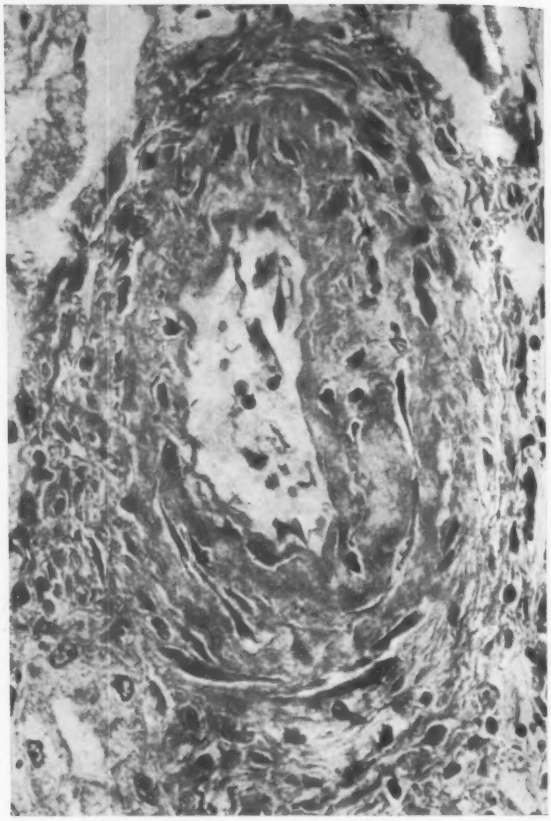

FIG. 5.

FIG. 6.

FIG. 4.—Section of the right kidney showing well-marked fibrohyaline thickening of the walls of the smaller arteries. Haematoxylin and eosin × 100.

FIG. 5.—High-power view of one of the smaller arteries seen in Fig. 1. Haematoxylin and eosin × 400.

FIG. 6.—Section of the left renal artery at its origin showing the marked fibrous intimal hyperplasia with considerable narrowing of the lumen. In addition a recent ante-mortem thrombus is present on the right of the photograph. Haematoxylin and eosin × 25.

sened, the blood urea level was 295 mg./100 ml., the total daily output of urine 180 ml. (protein present, and specific gravity 1006). The patient was put on to Bull, Joekes and Lowe's (1949) diet, but she deteriorated further, becoming incontinent of urine on the eleventh post-operative day, passed loose melaena stools, and became comatose, the blood urea having risen to 315 mg./100 ml. The serum sodium level remained low (118 mEq.), the potassium level was 4·0 mEq./litre and the CO_2-combining power 14 mEq./litre. Further administration of intra-gastric drip feeds was prevented by persistent vomiting, and no improvement resulted from intravenous administration of sodium chloride solution and blood transfusion. She died on the seventeenth day after operation with signs of uraemia and left lower lobe pneumonia.

Post-mortem Findings

External Examination. The body was that of a thin, female African child, with a recent left paramedian supra-umbilical surgical incision 4½ in. long.

The Left Kidney. The left kidney had been surgically removed before death as is described above. The left renal artery had been surgically ligated with catgut 2 cm. from its origin. At its origin from the aorta and for a distance of about 5 mm. the vessel was markedly narrow, being about 1 mm. in diameter. Distal to this narrowing the vessel was of normal calibre and contained a recent ante-mortem red thrombus. The aorta in the region of the origin of the left renal artery showed mild fatty streaking, the streaks being distal to the ostium.

The Right Kidney. The right kidney, 70 g., showed marked pallor of both cortex and medulla but no other significant lesion. The right renal artery contained a recent ante-mortem red thrombus about ¼ in. long.

The Bladder. The bladder showed an acute cystitis.

The Heart. The heart, 150 g., was markedly enlarged due to concentric hypertrophy of the left ventricle. On section the myocardium appeared healthy (left ventricle 11 mm., right ventricle 1 mm.). There was no obvious lesion in the valves and endocardium. The coronary arteries were healthy. The ductus arteriosus and foramen ovale were both closed. The pericardial sac was normal. The pleural cavities contained a slight excess of straw-coloured fluid and the lungs (R. 160 g., L. 110 g.) showed marked congestion.

The Peritoneal Cavity. This showed an acute generalized peritonitis.

The Liver. The liver, 800 g., presented a yellowish-brown appearance suggestive of diffuse fatty change.

Microscopic Examination

The Right Kidney. The right kidney showed marked fibrohyaline thickening of the walls of the smaller arteries. The afferent arterioles appeared normal. In addition an occasional glomerulus was hyalinized and many of the tubules were dilated and contained hyaline casts. The features were those of a severe nephrosclerosis (Figs. 4 and 5).

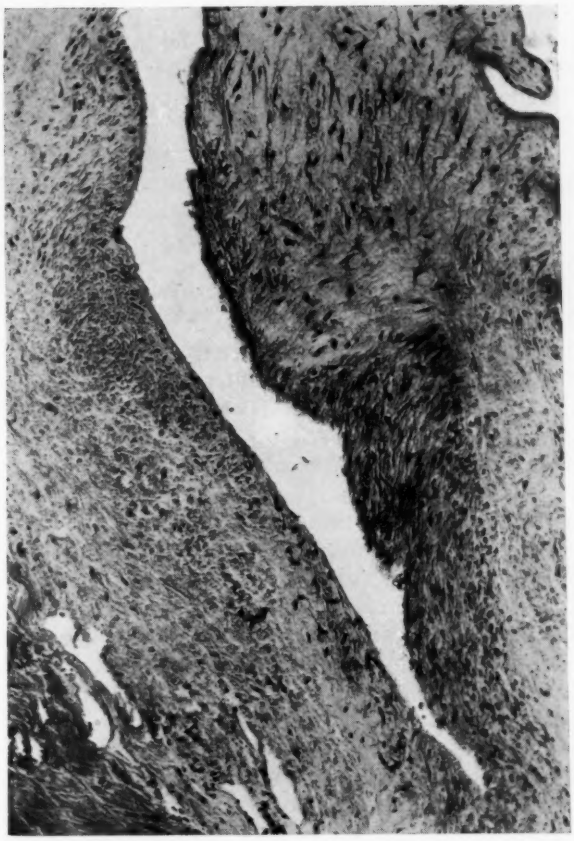

FIG. 7 —High-power view of the left renal artery showing the marked fibrous thickening of the intima. Haematoxylin and eosin × 100.

Right Renal Artery. The right renal artery showed considerable fibrous intimal hyperplasia and contained a large recent ante-mortem thrombus.

Left Renal Artery. Serial sections of the left renal artery showed marked thickening of the wall at its origin with considerable diminution in the size of the lumen due to old fibrous intimal hyperplasia. In addition, a recent ante-mortem thrombus was also observed. Beyond this area the lumen was of normal diameter (Figs. 6 and 7).

The Heart. The heart on section showed marked hypertrophy of the muscle fibres of the left ventricle.

The Liver. The liver showed diffuse fatty change, and section of the peritoneum showed the histological features of an acute peritonitis.

Discussion

Although no foci of fibrinoid necrosis were observed in the arterioles or glomeruli of the right

kidney, we feel that the presence of papilloedema and exudates with failing vision, and the severity of the hypertension justify, on clinical grounds, the diagnosis of malignant as opposed to benign hypertension.

The pathogenesis was almost certainly that of a partial obstruction to the left renal artery producing ischaemia of the left kidney with release of pressor substance and resulting hypertension. The marked nephrosclerotic changes produced in the right kidney were not present in the left kidney, as the latter was protected from the effects of the hypertension by the narrowed left renal artery. In effect this case was the human counterpart of the animal experiments of Goldblatt (1948) and Wilson and Byrom (1939). The aetiology of the fibrous intimal thickening of the left renal artery was not clear but may have been due to organization of an old thrombus or a reaction to anoxia.

According to Braasch (1942) less than 1% of patients with hypertension are amenable to therapy for hypertension by nephrectomy, and of 198 patients with hypertension due to unilateral kidney disease who underwent nephrectomy, 65 showed normal blood pressures post-operatively for one year or more. Allen (1952) states that the frequent failure to relieve hypertension by surgical removal of an abnormal kidney is probably due to the development of arteriosclerotic lesions in the opposite normal kidney as a result of the hypertensive state. It is theoretically possible that in such instances an earlier nephrectomy might prevent the development of contralateral renal arteriosclerosis with the resultant vicious circle of hypertension, renal ischaemia and more hypertension. It is clear then that nephrectomy in unilateral kidney disease can only bring relief of hypertension if the condition is discovered early. Depending, moreover, on the state of the retained kidney, hypertension may occasionally be made worse by nephrectomy. It is in such cases that renal biopsy may be of great value, and would in our case, for example, have clearly demonstrated the severity of the arterial lesions in the right kidney and the futility of left nephrectomy. Taken in conjunction with the intravenous pyelogram such a biopsy finding would have suggested, instead, an exploratory laparotomy to assess the state of the left kidney and renal artery.

Summary

A case of malignant nephrosclerosis in a child due to partial occlusion of the left renal artery is described. Whereas the right kidney showed severe nephrosclerosis, the left kidney presented minimal histological changes. In addition there was generalized arteriosclerosis with left ventricular hypertrophy. The patient died from acute peritonitis following removal of the left kidney. It is suggested that renal biopsy may be of value in such cases.

We wish to thank Dr. J. Benatar, Senior House Physician, for considerable personal endeavour, and the photographic department of the South African Institute for Medical Research for the photomicrographs. Mr. C. D. Kisner operated and Dr. H. Clain made the radiological examinations.

References

Allen, A. C. (1951). *The Kidney*. New York.
Braasch, W. F. (1942). *Canad. med. Ass. J.*, **46**, 9.
Bull, G. M., Joekes, A. M. and Lowe, K. G. (1949). *Lancet*, **2**, 229.
Goldblatt, H. (1948). *The Renal Origin of Hypertension*, pp. 18 and 33. Publ. No. 14, American Lecture Series. Springfield, Illinois.
Manners, T. (1954). *J. Path. Bact.*, **68**, 63.
Wilson, C. and Byrom, F. B. (1939). *Lancet*, **1**, 136.

PERTUSSIS ANTIBODY RESPONSE AFTER TRIPLE ANTIGEN

BY

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In the search for safe methods of immunization it must not be forgotten that the primary object of the procedure is to protect against a particular disease. As the minimizing of undesirable side-effects is obviously most important the safest antigens may be those in which potency has been reduced. For some time it has been found useful to add alum to pertussis and diphtheria antigens and this has increased their potency, but with improvements in preparation pertussis vaccine has been prepared in saline suspension and excellent results obtained. The addition of diphtheria toxoid to a pertussis antigen has been found to potentiate the antigenic power of the diphtheria toxoid (Ungar, 1952).

With the introduction of triple antigens the problem of antagonism was raised (Barr and Llewellyn-Jones, 1953), and care was needed to arrange the various constituents in such proportion that a response was obtained to all three antigens sufficient to produce immunity to each. Such preparations are in existence and have been used satisfactorily, but most have contained a mineral carrier.

Because of the fear of local complications and, more especially, on account of the fear of precipitating paralysis in a child affected by anterior poliomyelitis (Martin, 1950; McCloskey, 1950; Geffen, 1950; Bradford Hill and Knowelden, 1950) the use of irritant vaccines containing alum is being discontinued. The problem of whether saline vaccines are sufficiently potent antigenically with regard to each of the three constituents, pertussis, diphtheria and tetanus, must therefore be considered. It was with this problem in mind that the following investigation was undertaken.

Infants attending a routine follow-up clinic in the University Department of Child Health in Manchester were immunized with one of two vaccines, each comparable in the antigenic content of pertussis, diphtheria and tetanus, but one was in saline suspension and the other contained aluminium phosphate. Three injections were given to each infant at monthly intervals, the first being given when the infant was about 3 months old. Blood was taken by venipuncture one month after the third injection and antibody estimations were carried out, pertussis agglutinins, diphtheria antitoxin and tetanus antitoxin being measured. The results obtained are shown in Table 1.

The results show considerable individual variation

TABLE 1
RESULTS WITH PLAIN AND ALUM-CONTAINING VACCINES

	Pertussis Agglutination Titre	Diphtheria Antitoxin (units/ml.)	Tetanus Antitoxin (units/ml.)
Alum			
1	1/64	0·13	0·40
2	1/64	0·13	0·10
3	1/128	1·35	0·60
4	<1/16	0·525	0·80
5	1/128	0·68	0·10
6	1/512	3·60	0·60
7	1/64	1·05	0·60
8	1/128	0·53	0·60
9	1/32	1·40	4·0
10	1/1,024	0·70	1·00
11	1/16	1·05	0·9
12	1/512	1·05	0·45
13	1/64	0·175	1·05
14	1/16	0·044	0·05
15	1/512	0·525	1·00
16	1/512	1·05	0·80
17	1/128	0·375	0·80
18	1/16	1·20	2·0
19	1/128	0·263	0·10
Plain			
1	1/32	0·14	0·02
2	1/16	0·044	0·01
3	<1/16	0·70	0·20
4	<1/16	1·35	0·10
5	1/128	2·10	0·10
6	<1/16	0·70	0·10
7	<1/16	0·13	G·10
8	<1/16	0·24	0·40
9	1/64	0·13	0·10
10	1/1,024	1·05	1·5
11	No serum	0·525	0·45
12	1/1,024	0·525	2·0
13	1/512	2·40	1·60
14	<1/16	0·05	<0·02
15	1/16	4·20	2·00
16	<1/16	1·05	0·30
17	1/64	0·125	0·20
18	<1/16	1·80	1·60
19	<1/16	1·80	1·00
20	<1/16	1·80	2·00
21	1/16	1·50	2·00
22	<1/16	<0·0035	0·10

TABLE 2

Vaccine	No. Tested	No. of Children with Diphtheria Antitoxin Level of					
		<0·5	0·5–1·0	1·0–2·5	2·5–5·0	5·0–10·0	10·0–20
A	22	8	4	9	1	—	—
B	19	6	5	7	1	—	—
C	34	0	1	2	9	15	7

TABLE 3

Vaccine	No. Tested	No. of Children with Tetanus Antitoxin Level of			
		<1·0	1·0–5·0	5·0–10·0	10
A	22	14	8	—	—
B	19	14	5	—	—
C	33	0	17	14	2

TABLE 4

Vaccine	No. Tested	No. of Children with Pertussis Agglutination Titre of									
		<1/16	1/16	1/32	1/64	1/128	1/256	1/512	1/1,000	1/2,000	1/4,000
A	21	11	3	1	2	1	0	1	2		
B	19	1	3	1	4	5	0	4	1		
C	35	2	0	0	1	1	2	4	10	11	4

A = Plain vaccine at monthly intervals. B = Alum vaccine at monthly intervals.
C = Alum vaccine; third injection four to five months after second.

in response but if each type of vaccine is considered, together with response to the separate constituents, certain points of interest arise.

The alum-containing vaccine produced what is probably an immune level of antibody to the diphtheria and tetanus toxins. It also produced a measurable level of agglutinating antibody to pertussis in all but one child. On the other hand with the plain vaccine, although the level of diphtheria and tetanus antitoxins produced is probably adequate in all but one child, the production of agglutinating antibody to pertussis does not seem so satisfactory; of the 22 children in this group, 11 (50%) did not produce a measurable level of agglutinating antibody.

If we ignore the difference in titre of diphtheria and tetanus antitoxin in the two groups, as the levels in almost every group are sufficient to promise immunity, the response to pertussis agglutinogen should be studied. Here an alarming situation has arisen—if the power to produce agglutinins bears any relationship to the power to produce immunity. Although all but one of the children (approximately 95%) given the alum-containing vaccine responded, 50% of the children given the plain vaccine did not. Have we any proof of an immune response as an isolated reaction to a whole pertussis antigen? Until such a demonstration has been made there can be no justification for using an antigen of such reduced potency unless the dangers attached to the mineral-containing vaccine are excessive. The danger of local reaction is slight if a correct technique is used and the occasional abscess and pain are not sufficiently serious to justify the discontinuing of the alum vaccines. What then of the dangers of poliomyelitis? The policy of health authorities at present is to discontinue all immunization procedures during an epidemic and this is probably the wisest plan (Ministry of Health, 1952). Although less irritant injections are not so likely to cause paralysis the danger still exists in a minor degree. Surely another danger may be produced by using an uncertain vaccine, namely one of false security against pertussis, a disease less publicized than poliomyelitis but with a high morbidity of its own. In addition, the use of such an inadequate antigen may bring discredit on immunization in general.

A further point of interest arises when the results obtained in this series are compared with a previously published series (Feldman, 1954) in which the third injection was delayed until four to five months after the second. The antibody levels when obtained were greatly in excess of those in the present series with the three injections given at monthly intervals. The vaccine used in this previous trial differed in containing twice as much aluminium phosphate as the mineral-containing vaccine used in the present series. However, a comparison of results is justifiable as it is unlikely that the marked difference in antibody titre is entirely due to this and is much more probably due to the delayed third injection. Tables 2, 3 and 4 give a comparison of the titres

obtained with the two vaccines used in the present trial (A, plain vaccine, B, aluminium phosphate vaccine), in which the three injections were given at monthly intervals, and the titres obtained in the previous trial in which a vaccine (C) containing aluminium phosphate was used. In this last series the first injection was given at about 3 months of age, the second a month later and the third four to five months after the second. It will be seen that a higher mean titre is obtained to all three constituents when the third injection is delayed.

Summary

Results are presented obtained when comparable pertussis, diphtheria and tetanus triple antigens, one in saline suspension and the other containing a mineral carrier, were used in the immunization of two similar groups of infants.

Fifty per cent. of infants given the saline antigen failed to produce measurable titres of pertussis agglutinin.

The reasons for the use of plain antigens are discussed and considered insufficient to warrant their preference to the more potent alum-containing antigen.

Delaying the third injection until four or five months after the second produces a higher mean response to all three constituents.

My thanks are due to Professor Wilfrid Gaisford for his advice; to Dr. J. Ungar and Dr. P. W. Muggleton, of Glaxo Laboratories, who arranged for the antibody estimations to be carried out and made available the vaccines for the trial, and to Sister J. Boucock for her assistance.

References

Barr, M. and Llewellyn-Jones, M. (1953). *Brit. J. exp. Path.*, **34**, 12
Bradford Hill, A., and Knowelden, J. (1950). *Brit. med. J.*, **2**, 1.
Feldman, G V. (1954). *Archives of Disease in Childhood*, **29**, 175.
Geffen, D. H. (1950). *Med. Offr*, **83**, 137.
Hill, A. Bradford and Knowelden, J. (1950). *Brit. med. J.*, **2**, 1.
Martin, J. K. (1950). *Archives of Disease in Childhood*, **25**, 1.
McCloskey, B. P. (1950). *Lancet*, **1**, 659.
Ministry of Health (1952). Annual Report of the Chief Medical Officer for 1950. H.M.S.O.
Ungar, J. (1952). *Irish J. med. Sci.*, 6th ser., no. 316, p. 145.

ADRENOCORTICAL FUNCTION IN HYPERCALCAEMIA OF INFANCY

BY

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Since it is possible that adrenocortical hormones may be implicated in the regulation of calcium metabolism (see Hollinger and Pattee, 1956, for references) we considered that it would be of interest to gain some knowledge of the adrenocortical function of patients with idiopathic hypercalcaemia of infancy.

We have investigated two such patients, one having a severe hypercalcaemic syndrome similar to that described by Schlesinger, Butler and Black (1956) and another with the benign type of hypercalcaemia. The only practicable method of assessing the adrenocortical function of these infants was to determine the urinary excretion of adrenocortical steroids before and after the administration of A.C.T.H. Since little is known about the status of the adrenal cortex in infancy we have also investigated the urinary excretion of adrenocortical steroids by six normal children and by one child who had recovered from hypercalcaemia to provide values for comparison.

The results obtained from this preliminary investigation indicate that adrenocortical function in hypercalcaemic infants is impaired, and that the concentration of calcium in the blood of such infants can be influenced by adrenocortical hormones. These findings seem to us of sufficient importance to justify publication at this stage in spite of the limited scope of the investigation.

Methods

Both patients (C.I. and A.W.) were fed throughout the period of study on a low-calcium diet which analysis showed contained 220 mg. calcium per day. Urinary collections were made on a metabolic bed of the usual type and only complete 24-hour collections were analysed. Plasma calcium was estimated by the method of Clark and Collip (1925), plasma inorganic phosphorus by that of Fiske and Subbarow (1925), blood urea by that of Archer and Robb (1925) and plasma cholesterol by that of Sackett (1925). Plasma sodium and potassium were determined using the EEL flame photometer. Urinary calcium was estimated by the method of Shohl and Pedley (1922). Urinary 'total 17-ketosteroids' were determined in 24-hour urine specimens by the method of Norymberski, Stubbs and West (1953) as modified by Gibson and Norymberski (1954). In the A.C.T.H. test 1 unit of A.C.T.H. was given intramuscularly every four hours for 10 days unless otherwise stated. The same batch of A.C.T.H. was used for the two tests on C.I. and the first test on A.W. Another batch was used for the second test on A.W. In patient C.I. cortisone was given orally in two equal doses.

Results of Investigation of 'Total 17-Ketosteroid' in Urine of Six Normal Male Children

Four of the children were in hospital recovering from infection; their ages ranged from 3 to 18 months. Two children, aged 2 years, with no significant medical history were leading a normal life at home. No A.C.T.H. was administered to any of these children.

The mean excretion of urinary 'total 17-ketosteroids' in this group was 4·0 mg. per 24 hours, with a range of 3·5 to 5·2 mg. (11 determinations). It is this mean value which has been shown in Figs. 1, 2 and 3.

'Total 17-Ketosteroids' in Child Recovered from Hypercalcaemia. The male child who had recovered from hypercalcaemia was a full-term normal delivery. At the age of 6 months he was treated for meningococcal septicaemia but after discharge he became ill again and had a severe urinary infection; repeated subdural taps were negative. He did not thrive and had recurrent bouts of pyrexia which were only temporarily improved when treated with antibiotics. When he was 1 year old the plasma calcium concentration was found to be 16·0 mg. per 100 ml. and the blood urea level 101 mg. per 100 ml. A month later the plasma calcium had risen to 17·6 mg. per 100 ml. He was fed on a low-calcium diet and began to improve slowly; the plasma calcium fell to 12·7 mg. per 100 ml. and blood urea to 96 mg.

per 100 ml. On October 26, 1954, when he was aged 2 years, the plasma calcium and blood urea were 10·8 and 51 mg. per 100 ml. respectively. A 24-hour urine specimen was collected on September 10, 1956, when, at the age of 3 years 10 months, he was fit and well. His urinary excretion of 'total 17-ketosteroids' was 6·3 mg. per 24 hours, which is above the range of the six normal children, but as he was over a year older and had had hypercalcaemia he was not included in the normal series.

Patients' Reports

Case C.I. C.I., a boy, was born on May 17, 1955, a full-term normal delivery, birth weight 6 lb. Both parents and a sister were healthy. He was never breast fed but had Nestlé's (sweetened condensed) milk and 'ostermilk' (a full-cream milk) for three weeks. Because he vomited several times daily and was gaining weight only slowly he was changed to National dried milk. At the age of 4 months (September 27) he was admitted to hospital as he was only taking about 13 oz. of milk per day and was losing weight.

On admission he was a small infant weighing 9½ lb. He was not dehydrated. He had the characteristic facies seen in the severe type of hypercalcaemia of infancy. The skin of the trunk, limbs and face was light brown and the sclerae of the eyes blue, but no buccal pigmentation was seen. There was a loud precordial systolic murmur; his blood pressure was 160/100 mm. Hg. The urine was acid and contained a trace of albumin as well as casts and red and white blood cells; on culture *Escherichia coli* and *Proteus* were isolated. The blood white cell count was 11,450 per c.mm., and the Mantoux reaction was negative. Radiography revealed a marked increase of calcification of all bones, but there was no nephrocalcinosis. The concentrations of plasma calcium, sodium, potassium and of blood urea before and during the present investigation are shown in Table 1, together with plasma inorganic phosphorus and cholesterol concentrations which were also determined later in the investigation.

Treatment and Course. The infant was fed with a low-calcium milk with no added vitamin D. During the first months in hospital several phases of irregular pyrexia occurred. These were treated with sulphadimidine and streptomycin without improvement. His weight did not change significantly, and the hypercalcaemia persisted. In April, 1956, the plasma calcium concentration had fallen to 12·8 mg. per 100 ml. (see Table 1), but his condition was deteriorating clinically and it was then decided to begin investigation of adrenocortical function.

A.C.T.H. Test. During April and May two A.C.T.H. tests were carried out. The results of the tests, which consisted of the injection of 1 unit of A.C.T.H. every four hours for 10 days, are shown in Fig. 1. On neither occasion was there any significant increase in excretion of urinary 'total 17-ketosteroids', so that presumably there was no response to the A.C.T.H. (the slight apparent increase in 'total 17-ketosteroids' during the first test is probably not significant). There was no change in plasma calcium concentration during this period, as far as

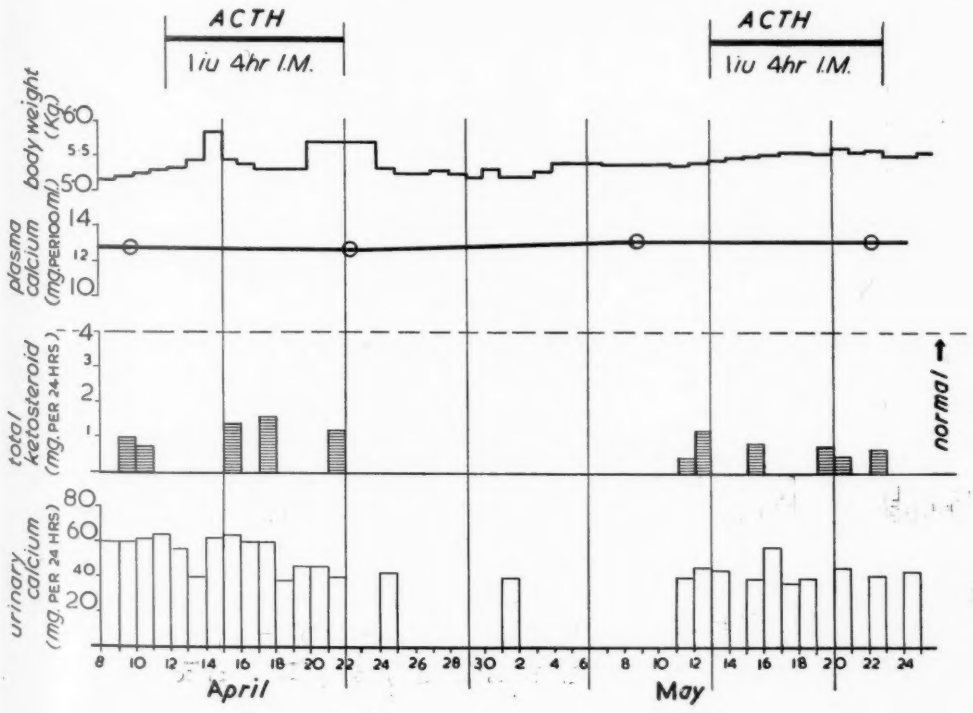


Fig. 1.—Response of patient C.I. to A.C.T.H.

TABLE 1
CONCENTRATIONS OF PLASMA CALCIUM, SODIUM, AND POTASSIUM AND BLOOD UREA IN CASE C.J.

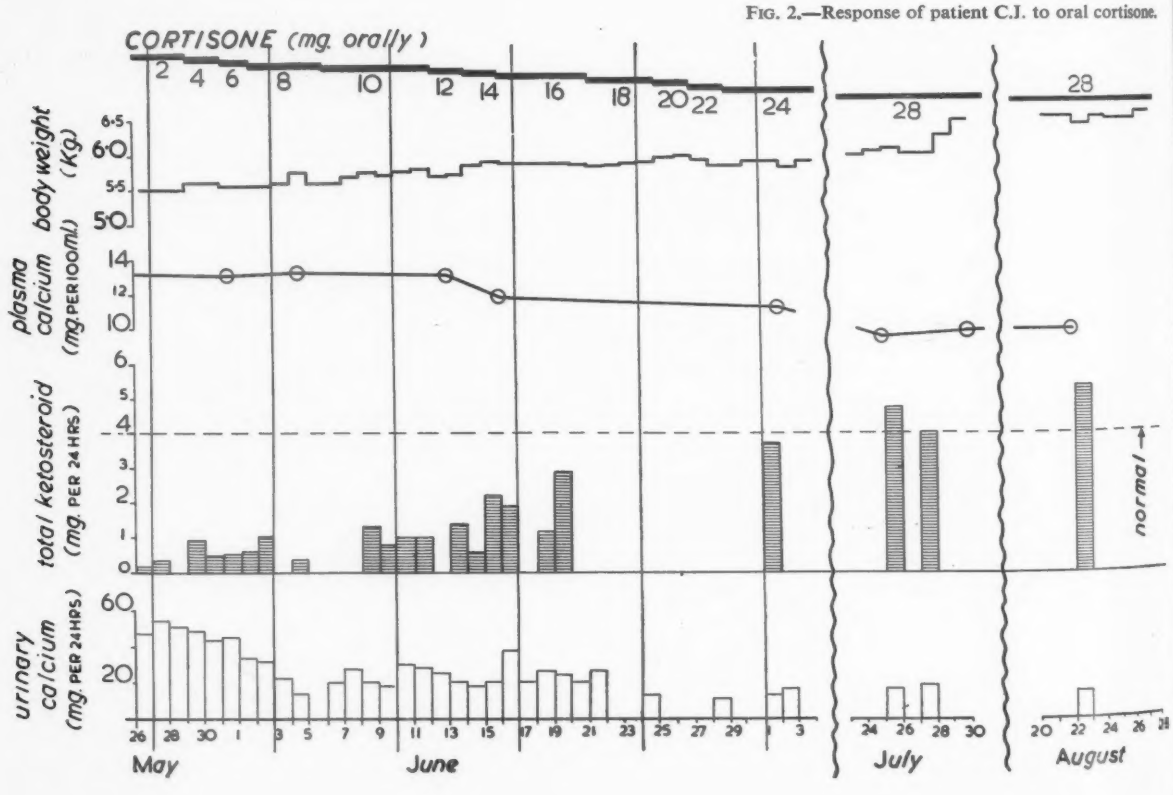
Date	Plasma Calcium (mg./100 ml.)	Plasma Inorganic Phosphorus (mg./100 ml.)	Plasma Sodium (mEq./l.)	Plasma Potassium (mEq./l.)	Plasma Cholesterol (mg./100 ml.)	Blood Urea (mg./100 ml.)	Remarks
20.10.55	14·7	—	154	5·0	—	146	
2.2.56	16·0	—	—	—	—	140	
9.4.56	12·8	5·7	152	3·2	—	76	On low calcium diet
12.4.56	—	—	—	—	—	—	A.C.T.H begun
21.4.56	—	—	—	—	—	—	A.C.T.H. ended
22.4.56	12·5	5·4	148	4·2	—	70	Day after cessation of A.C.T.H.
9.5.56	13·2	5·6	138	3·6	—	72	
13.5.56	—	—	—	—	—	—	A.C.T.H. begun
22.5.56	13·2	5·6	130	3·8	—	76	A.C.T.H. ended. Sodium chloride and potassium chloride begun
1.6.56	12·7	5·5	152	3·8	—	66	6 mg. cortisone o.d.
5.6.56	13·2	5·4	147	3·9	199	70	8 mg. cortisone o.d.
13.6.56	13·0	5·3	140	3·1	200	65	12 mg. cortisone o.d.
16.6.56	11·9	5·2	156	3·9	206	60	16 mg. cortisone o.d.
2.7.56	11·3	5·2	149	4·1	—	62	24 mg. cortisone o.d.
25.7.56	9·8	4·1	152	4·3	206	56	28 mg. cortisone o.d.
30.7.56	10·0	4·1	150	4·2	—	54	28 mg. cortisone o.d.
20.8.56	10·0	4·1	152	4·0	232	52	28 mg. cortisone o.d.

could be assessed by the limited number of blood samples available for analysis, but the urinary calcium concentration fell slightly during the first test. There were repeated sudden increases in weight which were not maintained, particularly during, and immediately after, the first test. Two weeks after the first A.C.T.H. test the infant developed a left-sided, lower motor neurone type facial paralysis which persisted for a month and then disappeared. Its occurrence was never satisfactorily explained.

After the second A.C.T.H. test the plasma sodium level was observed to have fallen to 130 mEq./l. and the plasma potassium level was 3·8 mEq./l. He was given 0·5 g. sodium chloride twice daily and 0·5 g. potassium chloride once daily; this treatment has been continued since then. Repeated determination of plasma sodium and potassium have shown concentrations within the normal range (Table 1).

CORTISONE ADMINISTRATION. In view of the lack of

FIG. 2.—Response of patient C.J. to oral cortisone.



response to A.C.T.H. it was decided to treat the infant with oral cortisone. To ascertain a dose which might reduce the plasma calcium concentration to normal and to prevent as far as possible any risk of overdosage the amount of cortisone administered was gradually increased from a starting level of 2 mg. per day. The output of urinary 'total 17-ketosteroids' while the infant was on this regimen is shown in Fig. 2. Blood analyses carried out during this period are given in Table 1. It can be seen that, as the dose of cortisone was gradually increased, (i) plasma concentrations of sodium, potassium and cholesterol did not change appreciably (Table I). (ii) The blood urea concentration gradually decreased (Table 1). (iii) Plasma concentrations of calcium, inorganic phosphorus and urinary calcium were markedly reduced, and there was a gradual increase in the weight of the infant. When the dose of cortisone had reached 28 mg. per day plasma calcium concentration became normal (Fig. 2 and Table 1). (iv) The excretion of urinary 'total 17-ketosteroids' gradually increased up to the level found in normal infants (Fig. 2).

During the administration of cortisone the pigmentation of the skin decreased considerably, but is still present. In spite of the disappearance of the hypercalcaemia the infant's development is grossly retarded. At 15 months he cannot sit up of his own accord, he makes only primitive noises, and is emotionally stunted. The fontanelle admits only the tip of the finger, and the sutures of the skull are rapidly fusing.

Case A.W. A.W., a girl, was born on May 22, 1956, a full-term normal delivery, birth weight 6 lb. 12 oz. Both parents and a sister were healthy. She was never breast fed, but developed well on National dried milk with the addition of one teaspoonful of cod-liver oil daily. At the age of 6 months she began to refuse feeds and to lose weight. Two months later she developed a cough and would sometimes vomit afterwards. Mixed feeding was tried but not tolerated and though bland feeds were taken without difficulty, she did not thrive.

On admission in March, 1956, at the age of 8 months, she weighed only 13 lb. 3 oz. and her muscles were hypotonic. The skin showed a diffuse, bright lemon-yellow coloration. The liver was palpable. The cardiovascular system, including blood pressure, was normal. The urine was acid, and though on occasions traces of albumin were found there was no significant number of white cells. Serum proteins were normal; radiography of the skeleton revealed no abnormality; the Mantoux reaction was negative. The concentrations of plasma calcium, inorganic phosphorus, sodium, potassium and cholesterol, and of blood urea before and during the present investigation are shown in Table 2.

Treatment and Course. During the first six weeks in hospital she had several attacks of pyrexia which subsided without chemotherapy. She was fed on a low-calcium diet and although feeding was satisfactory her weight did not increase nor was there any decrease in plasma calcium concentration. The yellow coloration of the skin decreased during this period but increased again during the first A.C.T.H. test.

A.C.T.H. Tests. The results of the two tests are shown in Fig. 3 and Table 2. It can be seen that, in the first test, (i) there was a marked fall in plasma calcium concentration and a definite increase in the urinary 'total 17-ketosteroids' to almost normal levels (Fig. 3). (ii) Administration of 24 units of A.C.T.H. per day did not appear to increase the response as judged by urinary 'total 17-ketosteroids' or plasma calcium concentrations, but there was a marked decrease in urinary calcium excretion associated with this larger dose (Fig. 3). (iii) The plasma inorganic phosphorus concentrations decreased (Table 2). (iv) There was a dramatic reduction in the concentration of plasma cholesterol (Table 2).

Associated with these changes was a great change in plasma sodium and potassium concentrations (Table 2). The infant appeared very well at this time but she has been given 0·5 g. sodium chloride since then, and her plasma sodium and potassium have remained at normal values. There was also a marked increase in blood urea during the test.

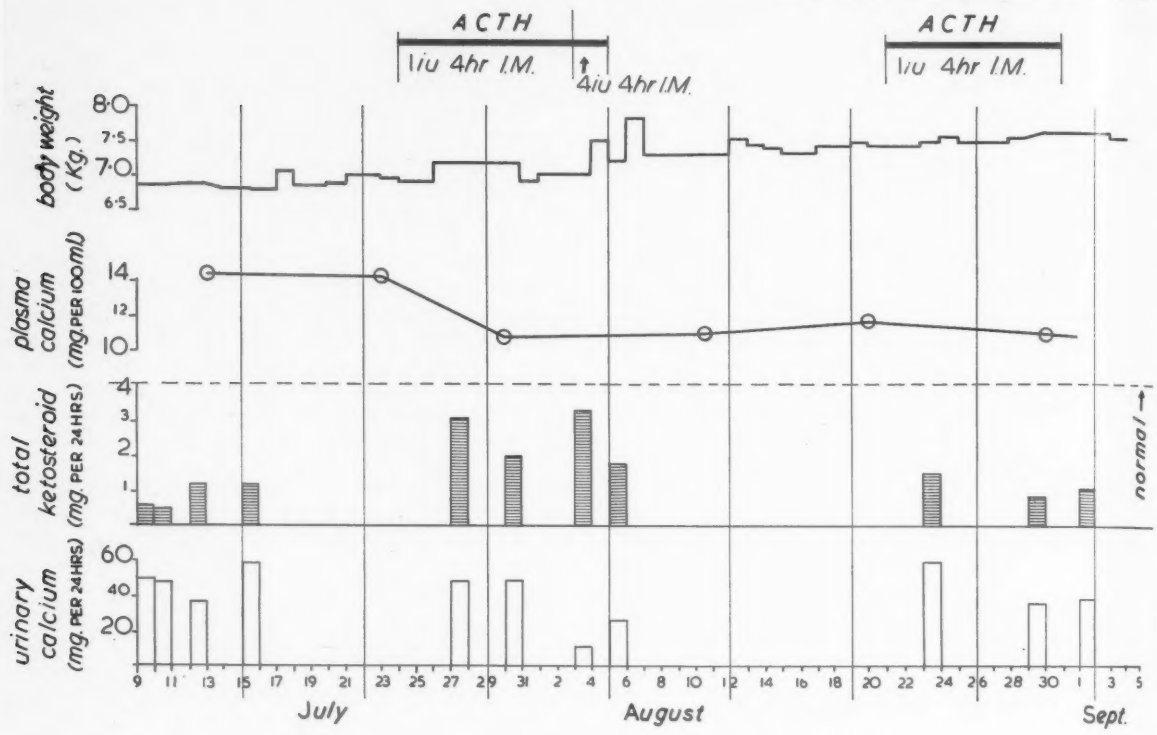
The failure of the second A.C.T.H. test to evoke a similar response may have been due to the fact that another batch of the hormone was used in this test.

Table 2

CONCENTRATIONS OF PLASMA CALCIUM, INORGANIC PHOSPHORUS, SODIUM, POTASSIUM AND CHOLESTEROL AND BLOOD UREA IN CASE A.W.

Date	Plasma Calcium (mg./100 ml.)	Plasma Inorganic Phosphorus (mg./100 ml.)	Plasma Sodium (mEq./l.)	Plasma Potassium (mEq./l.)	Plasma Cholesterol (mg./100 ml.)	Blood Urea (mg./100 ml.)	Remarks
29.2.54	—	—	—	—	440	130	
6.7.56	14·3	5·1	148	4·1	286	73	On low-calcium diet
13.7.56	14·3	5·0	152	4·2	280	53	
23.7.56	14·2	4·9	148	3·8	—	—	
25.7.56	—	—	—	—	—	—	A.C.T.H. test begun
30.7.56	10·8	4·3	109	5·0	121	133	During first A.C.T.H. test. Sodium chloride begun
5.8.56	—	—	—	—	—	—	A.C.T.H. ended
11.8.56	11·0	4·4	148	4·6	248	70	
20.8.56	11·8	4·8	152	4·2	256	66	
21.8.56	—	—	—	—	—	—	A.C.T.H. begun
30.8.56	11·0	4·8	150	4·0	274	55	During second A.C.T.H. test
31.8.56	—	—	—	—	—	—	A.C.T.H. ended

FIG. 3.—Response of patient A.W. to A.C.T.H



Since these tests the baby's condition has continuously improved. She is beginning to grow and gain in weight. She would always have been classed as a clinically moderate case, and it is felt that she will eventually become normal.

Discussion

The tests on patient C.I., who had the severe type of hypercalcaemia, showed that there was little or no adrenocortical response to A.C.T.H. Urinary 'total 17-ketosteroid' excretion remained low and there was no significant change in the concentrations of plasma calcium and inorganic phosphorus and blood urea; there was, however, a slight decrease in urinary calcium. These results suggest that the infant had a very much impaired adrenocortical function but it is also possible that the amount of A.C.T.H. administered was insufficient to stimulate the adrenal cortex. This possibility seems unlikely, however, in view of the dramatic response of patient A.W. to the same dose.

The response of patient C.I. to cortisone was very marked in contrast to his response to A.C.T.H. Plasma calcium and inorganic phosphorus and urinary calcium concentrations were gradually reduced, until at a dose of 28 mg. per day the plasma calcium concentration was normal. At the same time the urinary excretion of 'total 17-ketosteroids' gradually increased to just above the normal range (Fig. 2).

In contrast, the patient (A.W.) with the benign type of hypercalcaemia responded well to the first A.C.T.H. test as evidenced by the significant rise in 'total 17-ketosteroid' excretion, and by the dramatic fall in plasma calcium concentration. It will be noted that the plasma calcium concentration began to increase only very slowly when the A.C.T.H. was withdrawn. This response to A.C.T.H. suggests that in this infant the impaired adrenal function was secondary to failure of the pituitary to produce A.C.T.H. The impairment of adrenal function, whatever the cause, appears to be temporary, for most of the patients of her type make a complete recovery. Therefore it was not considered desirable to treat this patient with cortisone.

Creery and Neill (1954) and Forfar, Balf, Maxwell and Tompsett (1956) have found a high incidence of hypercholesterolaemia in hypercalcaemia of infancy. No mention was made by these authors of the effect of cortisone on plasma cholesterol concentration. Unfortunately determinations of the plasma cholesterol of patient C.I. were not made until treatment was begun, but in patient A.W. there was a striking fall in plasma cholesterol during the first A.C.T.H. test. Conn, Vogel, Louis and Fajans (1950) have

reported the same effect of A.C.T.H. on plasma cholesterol of adults.

While there are many possible explanations of the results obtained in these investigations we feel that at this stage speculation would be unwise. It does seem, however, that impaired adrenal function may be an important factor in hypercalcaemia of infancy. Furthermore, the evidence presented suggests that the infant with severe hypercalcaemia may have primary adrenal dysfunction while the case of the benign type may have secondary adrenal dysfunction. It is possible that there may be morphological changes in the adrenals or pituitaries of these patients but a survey of the recorded cases that have come to necropsy does not support this view.

Summary

Two infants, one with severe hypercalcaemia of infancy and the other with the benign type, had their adrenocortical function assessed by an A.C.T.H. test.

The infant with the benign type responded to the A.C.T.H. test as judged by the urinary 'total 17-ketosteroids' excretion and the restoration of plasma calcium concentrations. The severely hypercalcaemic infant did not respond to A.C.T.H. but his plasma calcium concentration became normal on treatment with 28 mg. cortisone per day.

It is suggested that impaired adrenal function may be an important factor in hypercalcaemia of infancy.

One of us, J.A., wishes to thank the Dean of Medicine for a personal grant. The success of the experiments was mainly due to the unceasing efforts of Sister J. Clayton and the nurses of Ward 7, Walkergate Hospital. Dr. M. Wallace gave valuable clinical assistance. Professor C. E. Dent kindly loaned us the rubber urine collectors. Mr. R. Richardson was responsible for providing the metabolic bed. Dr. R. D. Eastham and Miss C. A. Buchan gave valuable technical assistance.

References

Archer, H. E. and Robb, G. D. (1925). *Quart. J. Med.*, **18**, 274.
Clark, E. P. and Collip, J. B. (1925). *J. biol. Chem.*, **63**, 461.
Conn, J. W., Vogel, W. C., Louis, L. H. and Fajans, S. S. (1950). *J. Lab. clin. Med.*, **35**, 504.
Creery, R. D. G. and Neill, D. W. (1954). *Lancet*, **2**, 110.
Fiske, C. H. and Subbarow, Y. (1925). *J. biol. Chem.*, **66**, 375.
Forfar, J. O., Balf, C. L., Maxwell, G. M. and Tompsett, S. L. (1956). *Lancet*, **1**, 981.
Gibson, G. and Norymberski, J. K. (1954). *Ann. rheum. Dis.*, **13**, 59.
Hollinger, H. Z. and Pattee, C. J. (1956). *Canad. med. Ass. J.*, **74**, 912.
Norymberski, J. K., Stubbs, R. D. and West, H. F. (1953). *Lancet*, **1**, 1276.
Sackett, G. E. (1925). *J. biol. Chem.*, **64**, 203.
Schlesinger, B. E., Butler, N. R. and Black, J. A. (1956). *Brit. med. J.*, **1**, 127.
Shohl, A. T. and Pedley, F. G. (1922). *J. biol. Chem.*, **50**, 537.

ADRENAL NECROSIS IN GENERALIZED HERPES SIMPLEX

BY

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For a number of years after the first isolation of a virus from a case of human keratitis (Grüter, 1913, quoted by Lowenstein, 1919) the true nature of herpes remained in doubt because it did not seem to follow the hitherto accepted pattern of infectious disease (Doerr, 1938). But in 1938 Dodd, Johnston and Buddingh showed that herpes simplex virus could frequently be recovered from the saliva of cases of ulcerative stomatitis in children (Dodd *et al.*, 1938). These findings were confirmed the following year by Burnet and Williams who showed that after the acute phase of the illness herpes-neutralizing antibody appeared for the first time in the blood (Burnet and Williams, 1939). It was thus possible to distinguish between a primary herpetic infection in an individual with no previous immunity and a recurrent infection in which antibody was already present (Andrewes and Carmichael, 1930) and from these observations the modern concept of herpes as an infectious disease has developed (McNair Scott, 1954).

As in many other virus diseases inapparent infection is extremely common and it has been estimated that as many as 90 to 95% of all herpetic infections are asymptomatic (McNair Scott, 1954; Blank and Rake, 1955). In symptomatic infections the clinical picture is extremely variable both as regards site of infection and severity (Brain, 1956) and, also, children with eczema are particularly prone to develop a generalized infection due to virus dissemination. This is usually referred to as Kaposi's varicelliform eruption (K.V.E.) or eczema herpeticum. Many of these cases run a severe course (Jackson and Dudgeon, 1951). In recent years another and even more severe form of herpes has been recognized in which there is a fulminating infection with widespread visceral necrosis. Zuelzer and Stulberg first reported from the United States eight such patients among whom the most gross and widespread visceral lesions were found in a group of premature infants (Zuelzer and Stulberg, 1952). Subsequently, in this country, cases have been recorded of generalized herpes with hepatitis and encephalitis in newborn twins (France and Wilmers, 1953) and disseminated herpes with hepatic necrosis and isolation of virus from the liver at necropsy (Pugh, Newns and Dudgeon, 1954). However, visceral necrosis is not confined to this group of fulminating cases but may also occur in K.V.E. An instance of this was the finding of typical viral and atypical necrotic visceral lesions in a fatal case of K.V.E. seen in a small outbreak of herpes in a children's ward (Pugh, Dudgeon and Bodian, 1955).

The case described here is another example of fatal K.V.E. occurring in a ward for the treatment of skin disease, in which there were almost certainly two other cases of herpes simplex infection at the same time. After an illness which initially ran a not unusual course sudden deterioration with clinical evidence of adrenal insufficiency developed. At necropsy many necrotic lesions were discovered in both adrenals and herpes simplex virus was recovered from the adrenals, skin, brain, lymph nodes and uvula.

Case Report

P.G., a boy aged 9 months, was admitted to hospital on July 14, 1954, with a history of eczema, superimposed on a napkin erythema, since the age of 3 months. On admission weeping and crusted eczematous lesions were present on the trunk, face and limbs with enlargement of the lymph nodes but without obvious signs of secondary pyogenic infection. He was treated with saline baths and cooling lotions and for a time the skin lesions improved considerably. Later a relapse occurred and cortisone, 50 mg. daily, was given for three days but without effect. However, by the beginning of September the skin eruption had cleared except for some weeping lesions on the face which were then successfully treated with 1% hydrocortisone ointment locally.

On October 11 two other children (J.D. and A.W.) with 'infected eczema' were admitted to the ward and the possibility that they were suffering from herpes simplex infection was considered. In one case (J.D.) cytological evidence of herpes was found and the virus was sub-

FIG. 1.—The appearance of the skin lesions on the seventh day of the illness.

sequently isolated from the skin, but in the other (A.W.) the results of examination of the smears were equivocal. At this stage it was decided to give all patients in the ward gamma globulin as a prophylactic and, accordingly, this child (P.G.) was given 6 ml. intramuscularly (500 mg.) on October 15. On the following day he developed a typical herpetic eruption on the face, back and legs. His white blood count was 15,500 per c.mm. (neutrophils 87%) and coagulase-positive staphylococci and *Streptococcus haemolyticus* were cultured from the skin lesions. Antibiotic treatment was started and during the subsequent 10 days the child received 3·4 g. of aureomycin, 8½ million units of 'penidural' and 2 g. of 'gantrisin'. A further dose of gamma globulin (500 mg.) was given on October 18. The diagnosis of K.V.E. was confirmed by the finding of multinucleate epithelial cells in the vesicular lesions. The appearance of the skin condition at this time is shown in Fig. 1.

By October 20 the child's temperature had settled and his general condition was slowly improving. But five days later there was a sudden deterioration and collapse with dyspnoea, a distended abdomen and signs of severe shock. Investigations showed a total white blood count of 5,600 per c.mm. (neutrophils 65%), normal blood chemistry and a sterile blood culture; the blood sugar level was also normal. The baby did not respond to treatment, the systemic collapse persisted and he died on October 27, 1954, 11 days after the onset of K.V.E. Fig. 2 illustrates the course of the illness.

Laboratory Investigations

The methods of investigation used in this case have been described fully elsewhere (Dudgeon, 1951; Pugh *et al.*, 1955). The initial clinical diagnosis of herpes simplex was confirmed by the finding of multinucleate epithelial cells in scrapings from the vesicular skin lesions and by the isolation of herpes simplex virus by animal and egg inoculations. At necropsy, performed six hours after death, lesions suggestive of focal necrosis were noticed in both adrenals. The virus isolated from the various viscera was identified by histological examination and by the neutralization test in the chick-embryo. The results of these inoculations are summarized in the Table. The outstanding feature was the large amount of infective virus in the adrenals.

The virus isolated from skin, adrenals and brain was neutralized by specific herpes antiserum. Focal necrotic lesions with intranuclear inclusions were also found in the infected animal tissues. Neutralizing antibody (titre 1 : 16) was found in the child's serum collected at necropsy (11th day of the disease). Electrophoretic analysis of this same serum was carried out by Professor N. Martin at St. George's Hospital. The findings were: 'Pattern resembled that often seen in nephrosis, having a

TABLE

ISOLATION OF VIRUS FROM THE TISSUES

Inoculum	Chick-embryo Chorio-allantois (0·1 ml.)		Suckling Mice (intracerebral inoculation 0·05 ml.)	
	Focal Lesions	Average No. per Membrane*	Symptoms	Mortality Rate on Day 7†
Ante-mortem				
Skin swab	+	100–200	+	6/6
Vesicle fluid	+	100–200	+	6/6
Post-mortem				
Skin	+	100–200	+	5/6
Adrenal	+++	Confluent	+++	12/12
Brain	+	5–10	+	3/9
Lymph node	+	5–10	+	4/8
Uvula	+	5–10	+	5/6
Tracheal pus	—	0	—	0/6
Blood clot	—	0	—	0/6

* Number of focal lesions per membrane 48 hours after inoculation.
† Mortality rate in a litter of suckling mice on 7th day after inoculation.

low albumin and high alpha$_2$ globulin; the beta and gamma globulins being within normal range.' In interpreting these results it has to be recalled that 1,000 mg. gamma globulin had been given therapeutically 12 days before death.

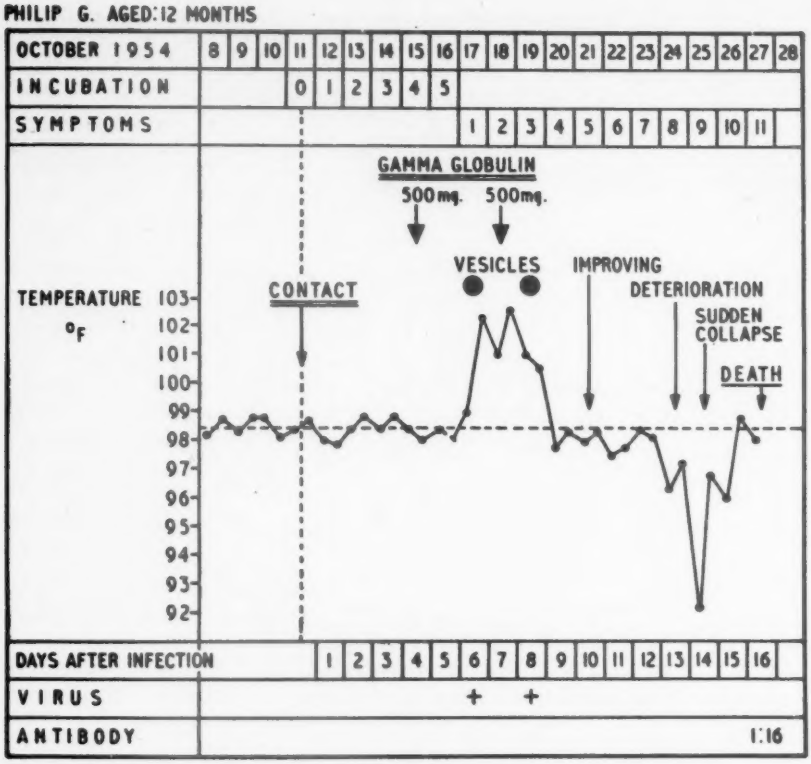
PHILIP G. AGED: 12 MONTHS
OCTOBER 1954
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
INCUBATION
0 1 2 3 4 5
SYMPTOMS
1 2 3 4 5 6 7 8 9 10 11
GAMMA GLOBULIN
500mg. 500mg.
VESICLES
IMPROVING
DETERIORATION
SUDDEN COLLAPSE
DEATH
CONTACT
TEMPERATURE °F
103 102 101 100 99 98 97 96 95 94 93 92
DAYS AFTER INFECTION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
VIRUS
+ +
ANTIBODY
1:16

FIG. 2.—Chart showing details of the clinical course and laboratory findings.

Post-mortem Appearances

The necropsy was performed six hours after death. The body was that of a male infant in good nutritional condition (height 30 in., body weight 19 lb.). There were extensive weeping and crusting eczematous lesions of the skin of the scalp, ears, face, neck, flanks, penis and scrotum, glutei and the whole of both lower limbs from the level of the inguinal ligaments downwards. Some lesions showed scaling and many of the smaller ones had serpiginous outlines. Flaccid, and sometimes umbilicated, vesicular lesions were present on both lower eyelids, in the right groin and on the fifth left finger. There was irregular desquamation of the skin of the upper limbs.

The brain weighed 950 g. and was intensely congested and moderately oedematous with some flattening of the convolutions at the occipital pole. Section confirmed the presence of congestion and oedema but did not reveal any other significant change. There was punctate congestion of the grey matter of the spinal cord. The right side of the heart was dilated. Rounded and irregularly-shaped areas of superficial ulceration, measuring up to 0·5 cm. in diameter, were found at the tip of the tongue and on the nasal surface and tip of the uvula. The pharynx and trachea contained rather viscid brownish mucoid exudate. The lungs were congested and oedematous without any obvious consolidation. The adrenals were of normal size and shape and their external surfaces were studded with large numbers of rounded or oval yellowish-white lesions, superimposed on a dark, reddish-purple background. Individually these measured between 0·1 and 0·3 cm. in diameter and were entirely cortical in situation, sometimes occupying the full thickness of the cortex and in other instances apparently lying more superficially (Fig. 3). The cervical, para-aortic, iliac and inguinal lymph nodes were enlarged and hyper-plastic. No other relevant abnormalities were found on internal examination.

Histology

Sections taken from all areas of the skin showed changes consistent with a chronic stage of eczema, with acanthosis, broadening of the rete pegs, hyperkeratosis and some lymphocytic infiltration in the more superficial parts of the corium. In addition, herpetic lesions were seen in all stages of evolution, varying from areas of early intra-epidermal vesicle formation to large areas of full-thickness necrosis of the epidermis. In all instances the lesions had clearly defined margins, showed a variable degree of secondary infection and had a superficial covering of crusted material. Unless there was a marked degree of secondary infection, polymorph infiltration was not a very conspicuous feature in any of the lesions. At the periphery of the vesicles and necrotic areas the intact epithelial cells frequently were multinucleate and enlarged—the so-called 'ballooned cells'—and both basophilic and acidophilic intranuclear inclusions, characteristic of herpes simplex, were seen. Similar necrotic and vesicular lesions, with intranuclear inclusions, occurred in the tongue and uvula, whilst in the lower part of the oesophagus there was a zone of full-thickness necrosis of the epithelium due to a local herpetic lesion. Both adrenals contained numerous clearly demarcated areas of recent coagulative parenchymal necrosis affecting the full thickness of the cortex. At the margins of the lesions there were small collections of polymorphs, together with some pyknotic nuclear debris (Fig. 4). In this area, too,

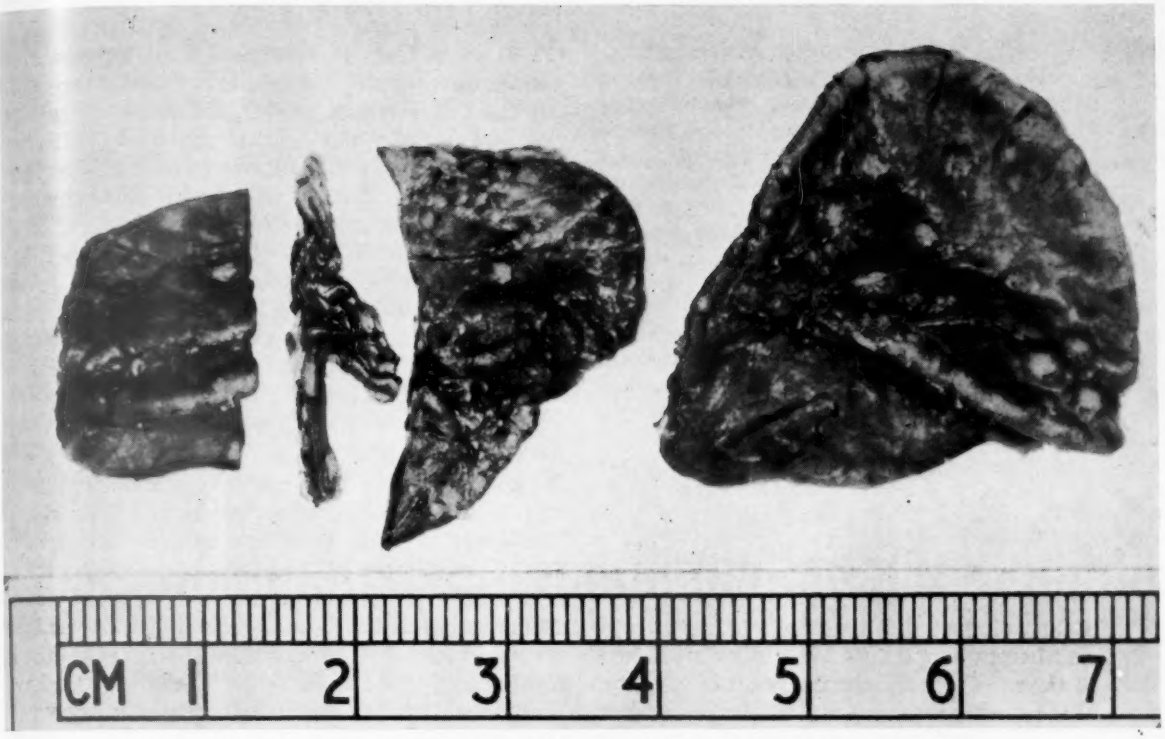

FIG. 3.—Adrenals: the numerous rounded pale lesions are visible on the external and cut surfaces.

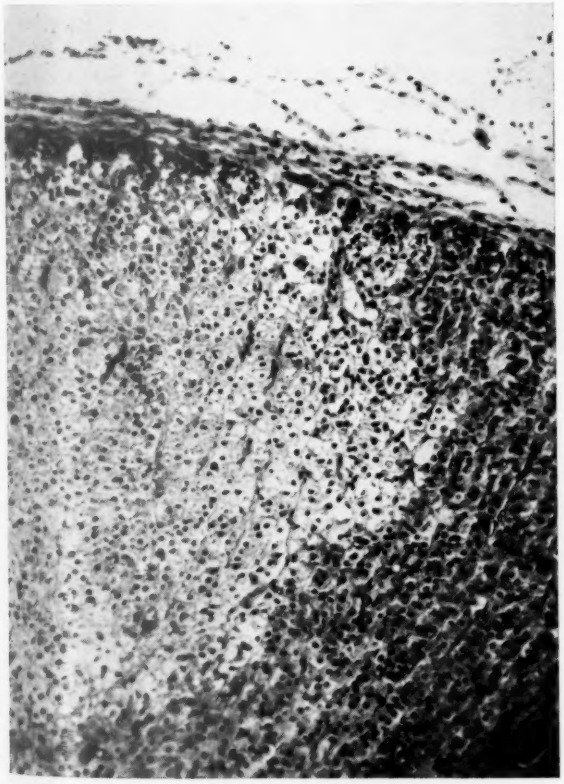

FIG. 4.—Adrenal: the margins of one of the viral lesions showing the clear line of demarcation between necrotic and living tissue.
Haematoxylin and eosin × 160.

FIG. 5.—Adrenal: high-power view of the margin of one of the necrotic lesions showing a typical intranuclear inclusion in the centre of the field.
Haematoxylin and eosin × 500.

many of the intact cortical cells contained basophilic or acidophilic intranuclear herpetic inclusions (Fig. 5). Many sections from representative areas in the brain and spinal cord failed to reveal any specific viral lesions, although at all levels there was a variable meningeal reaction, consisting of congestion and small aggregations of lymphocytes, as well as parenchymal damage, with chromatolysis of a considerable number of the ganglion cells. This was accompanied by a diffuse increase of round lymphocyte-like cells in the parenchyma and some perivascular cuffing of a few of the penetrating vessels with lymphocytes. These changes were particularly well marked in the cord, medulla and pons. No inclusions could be found. The lymph nodes showed well marked lymphoid hyperplasia and some patchy sinus catarrh, whilst in some nodes there was an accumulation of polymorphs and eosinophilic debris in the peripheral sinuses; no specific viral lesions were seen. The upper lobes of both lungs contained a few small foci of early bronchopneumonic consolidation.

Discussion

This infant died at the age of 12 months from generalized herpes simplex (K.V.E.) after an illness lasting 11 days. From the clinical point of view the course of the disease was unusual, as were a number of the laboratory findings.

The baby became infected with herpes simplex virus whilst in hospital for treatment of eczema and for just over a week the disease ran a perfectly normal course for an attack of K.V.E. But on the eighth day after the probable date of exposure, when the infection appeared to be resolving, the child suddenly became acutely ill again with clinical signs of adrenal insufficiency which persisted until death two days later. This is, in our experience, a most uncommon clinical course for a generalized herpetic infection in a child of this age. Moreover, we have not been able to find any similar accounts in the literature except that, in the series reported by Zuelzer and Stulberg (1952), three of the cases showed signs of acute shock just before death. In most cases of K.V.E. the severity of the infection is related to the size of the area of skin involved and to the toxaemia resulting from both viral and heavy secondary bacterial infection. In this case the skin lesions, although extensive, were healing when the systemic collapse occurred, so that it seemed certain that some serious complication, such as widespread visceral involvement or massive invasion of an important internal organ, had occurred. Post-mortem examination showed that this was in fact the case for there were viral lesions in many tissues, with particularly severe and extensive involvement of the adrenals.

Adrenal lesions are by no means unknown in herpes simplex and were first described by Hass (1935) in a case of hepato-adrenal necrosis in a premature infant. Other reports are those of Quilligan and Wilson (1951), Zuelzer and Stulberg (1952), Pugh *et al.* (1954) and Pugh *et al.* (1955), but this present case is the first one in which it has been possible to recover the virus from the affected gland. This may well be due to the heavy concentration of virus in the adrenal and to the fact that only six hours elapsed between death and necropsy. Also special precautions were taken to ensure that material for virus isolation was collected and stored under optimal conditions. In this connexion it may be significant that in the case reported by Pugh *et al.* (1955) the necropsy was not performed until 20 hours after death.

The reason for this marked involvement with such a heavy concentration of virus in the adrenals is difficult to understand and several factors have to be considered. First, the course of the infection might have been influenced by the use of cortisone but as this drug had been discontinued for several weeks before exposure to herpes this is highly improbable. Secondly, there might have been a defect in the immunity mechanism such as is known to occur in prolonged generalized vaccinia (Laurance, Cunliffe and Dudgeon, 1952; Hall, Cunliffe and Dudgeon, 1953), a condition characterized by a very much longer course with widespread visceral necrosis and associated with a complete failure of antibody formation and in some cases with agammaglobulinaemia (Keiden, McCarthy and Haworth, 1953). Again this seems unlikely in view of the short length of the illness, the presence of an inflammatory reaction in the skin and affected organs and the finding of a normal gamma globulin level in the blood. The diagnosis of agammaglobulinaemia and hypogammaglobulinaemia in the first year of life is unquestionably difficult as it seems probable that there is a condition of transient hypogammaglobulinaemia which arises from tardy development of gamma globulin rather than from any true defect in sensitivity. This transient condition is not, so far as we know, sex-linked and therefore appears to be different from the genetic agammaglobulinaemia described by Janeway *et al.* (Janeway, Apt and Gitlin, 1953). The normal range for gamma globulin for a 9-month-old child lies somewhere between 400 and 700 mg. per 100 ml. plasma. The total circulating globulin for a child of this size probably is a little over 1 g. If this child had been suffering from hypogammaglobulinaemia in the first instance it is quite possible that the 1 g. gamma globulin which was given therapeutically would have raised the calculated level to within the normal range, thereby masking an under-

lying hypogammaglobulinaemia (Martin, 1956). Interpretation of the serological test in which neutralizing antibody was found in a titre of 1:16 is also complicated by the injection of 1,000 mg. gamma globulin only a few days before the serum was collected at necropsy. Moreover, this coincided with the time that antibody can usually be detected in significant titre in herpetic infections and, on the face of it, it seems probable that some at least of this antibody resulted from active immunity.

The only conclusion that can be drawn is that for some reason the adrenals were the site of an unusual degree of virus multiplication, as a result of which their normal activity was impaired and the normal response to infection was overwhelmed by the concentration of infective virus produced.

The possibility that changes in the central nervous system might have contributed to death has also to be considered, particularly when it is recalled that the virus was recovered from the brain. Although no specific histological evidence of herpes in the form of intranuclear inclusions could be found, it is probable that the inflammatory changes that were present resulted from early viral invasion. Despite this there is little doubt that the adrenal lesions were more lethal than those in the nervous system.

It now has to be considered what steps can usefully be taken to reduce the risks of infection in subsequent cases of infantile eczema. Children with eczema, and particularly the very young ones, are so susceptible to herpetic infection that it would seem advisable to use every means possible to reduce the risk of exposure and subsequent infection. In a series of 16 cases of K.V.E. seen at The Hospital for Sick Children, 10 were under 1 year of age and nine were classed as seriously ill, although none died (Jackson and Dudgeon, 1951). In a more recent review of all cases of K.V.E. due to herpes simplex virus seen at this hospital from 1948 to 1956, a total of 36 cases was found of which approximately the same proportion were seriously ill. There were three deaths, including the case now reported (Brain, 1956). The source of infection is of the greatest importance and, in exactly the same way as efforts are made to avoid bringing eczematous children into contact with vaccinia virus by postponing vaccination, so should the risk of exposure to herpes virus be minimized. Clearly this may be difficult as is shown in the case described here, where two cases of 'infected eczema' were admitted to the ward and in at least one of whom the diagnosis of herpes was confirmed later. Moreover, barrier nursing methods were in use in the ward. It is known from experience that the degree of contact need not be very close and, even under the best possible conditions, infection can be spread from one cubicle to another. The danger from recurrent herpes in those in close contact with these children, such as parents and medical and nursing staffs, is well known but there is always the added danger of transferring infection from one case to another unless the most scrupulous attention is paid to detail. It would probably be advisable to regard all cases of 'infected eczema' as potentially infected with herpes virus unless proved otherwise, and especially while laboratory tests are being carried out or where the results are equivocal.

The use of gamma globulin must also be discussed; in this case 1,000 mg. given four to seven days after exposure failed to prevent infection and the most likely explanation is that it was given too late. The incubation period of herpes varies between four and seven days but by the time the first dose was given (see Fig. 2) virus multiplication was almost certainly well advanced and, moreover, at this stage the virus would be largely intracellular and therefore beyond the reach of antibody. Gamma globulin, which contains herpes-neutralizing antibody, should prevent infection if given before or immediately after exposure; so that, depending on the individual circumstances and the age of the child, passive immunization with gamma globulin should be considered for cases of infantile eczema on admission to hospital. A reasonable dosage would be 0·1 ml. per lb. of body weight with a further similar dose four to six weeks later if the stay in hospital is likely to be prolonged. The chances of sensitization from repeated injections of gamma globulin are negligible. Passive immunization before exposure combined with chemotherapy to control secondary infection should reduce the risk of a generalized infection and the resulting toxaemia in infants at this vulnerable age.

Summary

A case is described of fatal generalized herpes simplex with extensive adrenal necrosis in a boy 9 months of age. An unusual feature was the sudden collapse with signs of adrenal insufficiency that occurred on the eighth day of the illness. Post-mortem examination showed evidence of visceral involvement with a particularly heavy concentration of virus in the adrenals. It is suggested that in certain circumstances infants or young children with eczema and likely to be exposed to herpetic infection should receive passive immunization with gamma globulin.

We should like to express our thanks to Dr. Arild Harboe of the State Institute of Public Health, Oslo

(Research Fellow, Virus Laboratory, St. George's Hospital Medical School, September-December, 1953), for great assistance with the virus isolation experiments, and to Professor Nicholas Martin, Department of Chemical Pathology, St. George's Hospital Medical School, for carrying out the electrophoretic analysis and for much helpful advice and criticism.

References

Andrewes, C. H. and Carmichael, E. A. (1930). *Lancet*, **1**, 857.
Blank, H. and Rake, G. (1955). *Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man.* Boston.
Brain, R. T. (1956). *Brit. med. J.*, **1**, 1061.
Burnet, F. M. and Williams, S. W. (1939). *Med. J. Aust.*, **1**, 637.
Dodd, K., Johnston, L. M. and Buddingh, G. J. (1938). *J. Pediat.*, **12**, 95.
Doerr, R. (1938). In *Handbuch der Virusforschung*, ed. Doerr, R. and Hallauer, C., Vol. 1, p. 41. Vienna.
Dudgeon, J. A. (1951). *Gt Ormond Str. J.*, **1**, no. 1, p. 1.
France, N. E. and Wilmers, M. J. (1953). *Lancet*, **1**, 1181.
Grüter (1913). Quoted by Löwenstein (1919). Personal communication.
Hall, G. F. M., Cunliffe, A. C. and Dudgeon, J. A. (1953). *J. Path. Bact.*, **66**, 25.
Hass, G. M. (1935). *Amer. J. Path.*, **11**, 127.
Jackson, A. D. M. and Dudgeon, J. A. (1951). *Gt Ormond Str. J.*, **1**, no. 2, p. 125.
Janeway, C. A., Apt, L. and Gitlin, D. (1953). *Trans. Ass. Amer. Phys.*, **66**, 200.
Keiden, S. E., McCarthy, K. and Haworth, J. C. (1953). *Archives of Disease in Childhood*, **28**, 110.
Laurance, B., Cunliffe, A. C. and Dudgeon, J. A. (1952). *Ibid.*, **27**, 482.
Löwenstein, A. (1919). *Munch. med. Wschr.*, **66**, 769.
Martin, N. H. (1956). Personal communication.
Pugh, R. C. B., Dudgeon, J. A. and Bodian, M. (1955). *J. Path. Bact.*, **69**, 67.
——, Newns, G. H. and Dudgeon, J. A. (1954). *Archives of Disease in Childhood*, **29**, 60.
Quilligan, J. J. and Wilson, J. L. (1951). *J. Lab. clin. Med.*, 38, 742.
Scott, T. F. McNair (1954). *New Engl. J. Med.*, **250**, 183.
Zuelzer, W. W. and Stulberg, C. S. (1952). *Amer. J. Dis. Child.*, **83**, 421.

A CLINICAL STUDY OF THE ABDOMINAL SKIN REFLEXES IN NEWBORN INFANTS

BY

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The abdominal skin reflexes have been shown to be present in children and adults with a definite pattern of such constant appearance that they play a part in the routine clinical examination (Munch-Petersen, 1901; Müller and Seidelmann, 1905; Söderbergh, 1918). But, according to well known text-books on neurology and paediatrics, the examination of the abdominal skin reflexes in the newborn and infants is of very little clinical value because of their inconstant pattern. This common view may be illustrated by the following quotation from Ford (1952):

> 'The abdominal reflexes may be elicited in the newborn in about one-third of all cases. The reflex obtained at this age is a rather diffuse reaction often involving the extremities and probably essentially different from the adult response. Some time between the sixth month and the end of the first year the true abdominal responses should appear.'

DeJong (1955), Ellis (1951) and Nelson (1954) express a similar view.

The abdominal reflexes encountered in children and adults are by many authors supposed to be neo-flexes, that is, reflexes developed late in infancy and dependent on the functional state of the pyramidal tract (Bychowski, 1908; Monrad-Krohn, 1950). Most publications report findings supporting the view expressed by the authors previously mentioned.

Munch-Petersen (1901) could not elicit the abdominal reflexes in 19 of 65 children up to 2 years old, but he did not especially emphasize the findings in the newborn period. Cattaneo (1902) found the abdominal reflexes to be absent in the first month of life. In infants 5 to 90 days old he could find these reflexes present in 35% only. Laurent (1905) concluded after his investigation of 34 infants in the group aged 0 to 3 months that the abdominal reflexes are absent or weak in newborn infants. Bychowski (1908) examined 39 infants under 2½ years old, and found abdominal reflexes in only four of them. He claimed that these reflexes are not present at birth. Monrad-Krohn (1918) observed abdominal reflexes in about one-third of the infants examined. Griffith and Mitchell (1927) stated that according to Burr (1921), who examined 20 infants and found the reflexes absent in seven, the abdominal reflexes appear irregularly. Chaney and McGraw (1932) examined 25 newborn infants immediately after birth, finding abdominal reflexes in only two. Further, they examined 100 infants from 2 to 35 hours old, and observed these reflexes in only 33·3%, without being able to explain this low frequency. André-Thomas, Chesni and St. Anne Dargassies (1954) stated that the abdominal reflexes are not present in the first 10 days of life.

On the other hand, some authors report findings which indicate that the abdominal reflexes are present from birth. Goldflam (1912) examined 30 infants from 9 days to 1 year old. He elicited abdominal reflexes in all of them. He did not, however, describe the character of the response in detail. De Angelis (1923) examined 87 infants in the first week of life, most of them under 2 days old. He stated that, by waiting patiently for the right moment, one might succeed in eliciting all reflexes in the newborn. It seemed to us improbable that the abdominal reflexes should behave differently from other reflexes, and appear at an age when reflex activity otherwise diminishes, and a preliminary investigation of 28 infants in the Department of Paediatrics, Oslo University Hospital, seemed to indicate that abdominal reflexes of a definite pattern were constantly present in early infancy (Lönnum, 1956).

This and the previously reported investigations concerning the abdominal skin reflexes in infancy covered a comparatively small number of infants, and as the reports did not satisfactorily describe the responses in detail, a more comprehensive study was considered necessary.

The present study was undertaken with two

objects in view: (1) To examine the frequency of the abdominal reflexes in early infancy in a sufficiently great number of infants. (2) To get information of the character of these reflexes at this age.

Material

Two hundred healthy, full-term infants, 112 boys and 88 girls, were examined in the Department of Obstetrics of Oslo University Hospital. The youngest was 2 hours old, the oldest 7 days old. More than 50% were from 2 to 4 days old. The length of the boys varied from 43 to 57 cm., with an average of 51·5 cm. The average weight in this group was 3,475 g., varying from 1,770 (in the smallest twin) to 4,860 g. The average length of the girls was 50 cm., varying from 46 to 56 cm., and the average weight in this group was 3,435 g., varying from 2,480 to 4,480 g.

Methods

To obtain ideal conditions for the examination of the abdominal reflexes, the following examination alone was done.

The baby was placed on the nursing table in a quiet, warm room and was handled by a trained nurse. Uneasy or crying infants were given a nipple dipped in glucose solution. The abdominal reflexes were examined with the technique described by Monrad-Krohn (1918). For routine stimulus a blunt needle was used with strokes applied along the costal margin, in the supra-umbilical, umbilical and infra-umbilical region.

Results

Under such conditions and with this technique the abdominal reflexes were found to be present with a definite pattern in all the 200 infants examined.

A typical response consists of a segmental, homo- and uni-lateral deviation of the linea alba, of exactly the same character as in adults. There is further a curving of the trunk to the stimulated side, as observed in some cases by Monrad-Krohn (1918) and others. This curving is the result of a simultaneous visible and palpable contraction of the rectus abdominis muscle and the homolateral erector trunci muscle. There is a marked tendency to bilateral responses and to a retraction of the abdominal wall. The responses are more extensive and the reflexogenous zone is wider than in adults.

Almost immediately after the response described, a flexion in the homolateral leg or in both legs is observed, consisting of the same motor components as the well-known flexion reflex under pathological conditions. However, this flexion reflex in infants is characterized by shorter latency and duration than the pathological flexion reflex.

In some cases a series of pinpricks and spatula strokes were used as stimuli. The same responses were obtained as with the blunt needle which, however, was used as the routine stimulus for three reasons: (1) This stimulus was used in most of the earlier investigations of these reflexes. (2) It is preferred by most clinicians in the routine clinical examination. (3) It was found to be the most effective.

Sometimes the reflexes were readily elicited, but often one had to wait for minutes to obtain the right moment for applying the stimulus. The reflexes were weak in some cases, especially in uneasy infants and in infants with dry skins. In such cases a brisk response could be obtained after soothing the infant or after oiling the skin. Weak abdominal reflexes were also observed in infants with distended abdomen. In these cases the examiner had to wait until the distension was reduced.

Sometimes the segmental response was more readily elicited, sometimes the curving of the trunk or the flexion reflex. These partial responses were, however, in no way different from the reactions described in the typical response.

Discussion

Our investigation confirms the observations of Goldflam (1912) and De Angelis (1923) that the abdominal reflexes in man are present from birth. It does not support the view commonly expressed in text-books on neurology and paediatrics, probably based on the observations of Munch-Petersen (1901), Cattaneo (1902) and others. The discrepancies between the findings of the investigators mentioned earlier and ours might be explained partly by differences in methods.

The abdominal reflexes only were examined in the present investigation, whereas most of the aforementioned investigators seem to have made it a part of a broader examination. During a prolonged examination of an infant it is very difficult to keep optimal conditions throughout, and some of the results will necessarily be unreliable. In some cases we could not at first obtain good results because the infant was uneasy or cried, and therefore had to watch for the right moment. In other cases, a distended abdomen or a dry skin prevented a satisfactory response.

The positive result of our investigation may to some extent be dependent on the fact that our study was started on the presumption that the abdominal reflexes, as well as other reflexes, are present from birth. In doubtful cases this presumption would

stimulate greater patience during the examination.

The abdominal skin reflexes observed in early infancy have been thought to be essentially different from the responses observed in children and adults. Our findings do not support this view. A comparison between the ' normal ' adult response and that in infants indicates that the former is principally the same as the latter. The reflexogenous zone is narrower in adults and the response itself localized to muscles belonging to the stimulated segments. The most probable explanation of these facts is that in adults the response is inhibited compared with the response in infants. The abdominal reflexes therefore seem to be inhibited when cerebral control is developed as are other reflexes of the infant, e.g., the grasping reflex, the Moro reflex and the sucking reflex (Litvay, 1950; Lamote De Grignon, 1955). They cannot be neo-reflexes as Bychowski (1908) stated.

A curving of the trunk to the stimulated side is readily induced in infants by stroking the skin along the spine (Litvay, 1950). A similar curving was often observed when eliciting the abdominal reflexes. This reaction, which has earlier been described by Goldflam (1912), Monrad-Krohn (1918) and others, has in regards to stimulus, latency and duration much in common with the usual abdominal skin reflexes. The two reaction types are, therefore, in our opinion, of the same nature.

The abdominal skin reflexes have been thought to represent a reaction of defence (Karassik, 1924), but a defence reaction would most likely be the response to a nociceptive stimulus, whereas the abdominal skin reflexes are more readily elicited by a tactile stimulus (Monrad-Krohn, 1918). The response itself has the character of coordinated movements, as has the grasping reflex. The abdominal muscles have partly retained a segmental structure. It may be suggested that these primitive muscles have also retained primitive movement patterns. The abdominal reflexes may therefore represent remnants of segmental movements governed by external, tactile stimuli.

A flexion of the homolateral leg or of both legs was frequently observed simultaneously with, or immediately after, the abdominal reflexes. The motor components were the same as in the flexion reflex often elicited from the abdomen in adults in diseases of the central nervous system, especially in cases of transverse spinal lesion (Riddoch, 1917; Monrad-Krohn, 1925). However, the response in infants was of shorter latency and duration.

The difference in response may be explained by the presence of a supraspinal facilitating influence in infants, which is lost in patients with transverse spinal lesions. The abdominal, and particularly the flexion reflexes, are weakened in the course of infancy, probably because of the development of a central inhibitory mechanism. In certain cases of disease in the central nervous system in adults, a flexion reflex is observed simultaneously with brisk abdominal skin reflexes (Lönnum, 1956). This fact may be explained by a lesion which abolishes the inhibitory mechanism mentioned before.

From the work of Rosenbach (1876) it is known that the abdominal reflexes are altered in cases of cerebral lesions. It is therefore assumed that these reflexes are dependent on supraspinal structures. In the foetus abdominal reflexes have been observed which are supposed to be of purely spinal origin (Krabbe, 1912; Minkowski, 1923). However that may be in the foetus, the character of the abdominal reflexes in newborn infants is so similar to that in adults that a supraspinal influence must also be assumed at this stage. We have found abdominal reflexes absent in infants with cerebral lesions. This fact seems to corroborate the assumption that the abdominal reflexes in early infancy are dependent upon supraspinal structures.

As the pyramidal tract has been supposed to be necessary for the abdominal reflexes (Monrad-Krohn, 1950, and others), it has hitherto been difficult to explain the findings of brisk abdominal skin reflexes in diseases with lesions of this tract (Wartenberg, 1945). If the pyramidal tract really is essential to the abdominal reflexes, some fibres in it must necessarily function from birth. A lesion of these fibres may abolish the reflexes. According to the common view other fibres do not start functioning until about six months after birth. These fibres may be the transmitter of the inhibitory central influence upon the abdominal reflexes previously mentioned. A selective lesion of these fibres would explain the findings of brisk abdominal reflexes in cases of pyramidal tract involvement. Nathan and Smith (1955) have recently shown that the pyramidal tract is not the only tract of importance to the plantar reflex. This probably applies to the abdominal reflexes as well. Further clinical and experimental work is necessary to clarify the relationship between the abdominal reflexes and the pyramidal tract and other structures of the central nervous system.

Summary

According to well-known text-books on neurology and paediatrics, the abdominal skin reflexes in newborn infants are present only in a relatively small number of cases and are of an irregular pattern.

All of 200 full-term healthy infants in the first week of life were found to have abdominal skin reflexes of a definite pattern.

The theories concerning the abdominal skin reflexes are discussed.

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References

André-Thomas, Chesni, Y. and St. Anne Dargassies (1954). *Vie méd.*, **35**, Dec. Special No., p. 16.
Burr, C. W. (1921). *Amer. J. Dis. Child.*, **21**, 529.
Bychowski, Z. (1908). *Dtsch. Z. Nervenheilk.*, **34**, 116.
Cattaneo, C. (1902). *Jb. Kinderheilk.*, **55**, 458.
Chaney, L. B. and McGraw, M. B. (1932). *Bull. neurol. Inst. N.Y.*, **2**, 1.
De Angelis, F. (1923). *Amer. J. Dis. Child.*, **26**, 211.
DeJong, R. N. (1955). In A. B. Baker's *Clinical Neurology*, vol. I, p. 65. New York.
Ellis, R. W. B. (1951). *Disease in Infancy and Childhood*, p. 22. Edinburgh.
Ford, F. R. (1952). *Diseases of the Nervous System in Infancy, Childhood and Adolescence*, 3rd ed., p. 61. Oxford.
Goldflam, S. (1912). *Z. ges. Neurol. Psychiat.*, **8**, 230.
Griffith, J. P. C. and Mitchell, A. G. (1927). *The Diseases of Infants and Children*, 2nd ed., vol. I, p. 61. Philadelphia and London.
Karassik, W. M. (1924). *Pflügers Arch. ges. Physiol.*, 204, 549.
Krabbe, K. (1912). *Rev. neurol. (Paris)*, (Oct.), **24**, 434.
Lamote De Grignon, C. (1955). *Ibid.*, **93**, 217.
Laurent, R. (1905). *Evolution des réflexes chez l'enfant*. Thése, Toulouse.
Litvay, E. (1950). *Ann. paediat. (Basel)*, **174**, 252.
Lönnum, A. (1956). *Acta psychiat. neurol. scand.*, **108**, p. 243, Suppl.
Minkowski, M. (1923). *Schweiz. Arch. Neurol. Psychiat.*, **13**, 475.
Monrad-Krohn, G. H. (1918). *On Abdominal Reflexes*. Kristiania (Oslo).
—— (1925). *Arch. Neurol. Psychiat. (Chicago)*, **13**, 750.
—— (1950). *Schweiz. Arch. Neurol. Psychiat.*, **66**, 338.
Munch-Petersen, H. (1901). *Hudreflexerne og deres Nervebaner*. Copenhagen. Cited by Monrad-Krohn.
Müller, E. and Seidelmann, W. (1905). *Münch. med. Wschr.*, 52, 1323.
Nathan, P. W. and Smith, M. C. (1955). *Brain*, **78**, 248.
Nelson, W. E. (1954). *Textbook of Pediatrics*, 6th ed., p. 33. Philadelphia and London.
Riddoch, G. (1917). *Brain*, **40**, 264.
Rosenbach, O. (1876). *Arch. Psychiat. Nervenkr.*, **6**, 845.
Söderbergh, G. (1918). *Neurol. Zbl.*, **37**, 234.
Wartenberg, R. (1945). *The Examination of Reflexes*. Chicago.

CONGENITAL MALFORMATIONS OF THE HEART AND THE GREAT VESSELS ASSOCIATED WITH CONGENITAL ABSENCE OF THE SPLEEN

BY

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The unusual combination of congenital malformations of the heart and great vessels on the one hand, with agenesis of the spleen on the other hand has been looked upon as a great medical curiosity. In the past it had been the pathologist exclusively who from time to time encountered this association of anomalies. More recently, however, cases have been diagnosed by the clinician during the life of these patients.

The first case on record of this combination of anomalies is that of Martin (1826), who described the necropsy findings of a case of septal defects, transposition of the great vessels and agenesis of the spleen. Afterwards a number of other reports dealt with cardiac anomalies curiously associated with agenesis of the spleen. In 1934 Putschar reviewed the findings of all cases reported up to that time, collecting from the literature a total of 22 cases. The next review of the literature is that of Polhemus and Schafer (1952). These authors pointed out for the first time that these cases of cardiac anomalies associated with absence of the spleen actually constitute a definite syndrome. The latest review is that of Biorn Ivemark (1955) who collected all the cases reported in the literature since the very first case of Martin (1826) and added 14 more cases of his own.

The first two cases of agenesis of the spleen associated with cardiac anomalies diagnosed *in vivo* and confirmed at necropsy were those reported by Gasser and Willi (1952). They based their antemortem diagnosis on a persistently increased number of Heinz bodies in the erythrocytes of the peripheral blood.

Recently a case of agenesis of the spleen with multiple anomalies of the heart and the great vessels was observed in the Paediatric Department B of the Rambam Government Hospital in Haifa. In this paper we wish to report this case. We should also like to discuss the correlation of the clinical signs observed.

Case Report

S.Y., a white 10-day-old boy, was born in a private maternity clinic after a prolonged labour and with the aid of mid-forceps. On the day after birth the house physician observed that the child was cyanotic and cold. On the fifth day of life a systolic murmur was heard over the apex. The baby was then transferred to this Department for clinical appraisal.

The family history was negative for heart disease or congenital anomalies. The mother was a 22-year-old primipara primigravida. She denied any rashes or serious illnesses during the first trimester of this pregnancy.

When first seen in our Department the baby was found to be well developed and well nourished. His weight was 7·92 lb. The lips, ear lobes and nail beds were distinctly cyanotic and the skin had a rather bluish hue. The apex beat of the heart was felt on the right side of the sternum in the fourth intercostal space. The heart sounds were clear and heard best on the right side of the chest. There were no murmurs. The spleen and the liver were not palpable under the costal margin.

Laboratory examinations gave the following results: Hb 15·8 g. %, red blood cells 3,900,000/mm.^{3}, white blood cells 7,800/mm.^{3} (65% neutrophils, 6% eosinophils, 1% basophils, 8% monocytes, 19% lymphocytes and 2% plasma cells). Stools and urine were normal.

A radiograph of the abdomen showed the liver to be normally placed on the right and the stomach on the left. The radiological picture of the heart was considered to indicate dextrocardia confirming the clinical impression. The left lung was shadowed. A control examination a week later revealed shadows in both upper lobes.

An electrocardiogram on the eighth day of his hospital stay showed sinus tachycardia, with a rate of 140 per minute. There was no axis deviation. The heart was in the intermediary position (P-Q = 0·12 sec.; QRS = 0·07 sec.; QT = 0·24 sec.; R-P = 0·44 sec.). The Q wave was deep in leads I and II and less in aVF and aVL; the T wave was negative in leads I, aVL and biphasic (− +) in lead II. The S-T segment was elevated in V1 and V2, but less than 2 mm.; V1 and V2 showed an RS pattern and V5 qR pattern; the transitional zone

was between V3 and V4. This was interpreted as indicating a normal position of the heart chambers. The electrocardiographic diagnosis was probable tricuspid atresia, trilocular heart.

During the first week in hospital the patient exhibited intermittent attacks of cyanosis. Repeated physical examinations were considered essentially normal, except for the cyanosis. At no time were any abnormal neurological signs found and no marked respiratory embarrassment was noted.

Throughout this period the general condition of the child was satisfactory and he did not lose weight. His appetite was good. No drugs were administered during this period.

At the beginning of the second week in hospital signs of pneumonia of the left upper lobe were elicited on physical examination. Later on the baby developed diarrhoea and vomiting with secondary disturbances of the fluid and electrolyte balance. He was treated with oxygen, plasma, intravenous fluids and electrolytes, penicillin and streptomycin and oxytetracycline but he continued to do poorly. On the eve of his death a number of small fluctuant nodules appeared on the anterior chest wall. One of them, situated over the upper part of the sternum, showed clear pulsations, synchronous with the heart beat. This nodule was punctured immediately after death and pus withdrawn, and culture showed a pure growth of *Proteus vulgaris*. On the morning of his 31st day in hospital the patient expired.

Necropsy Report

The essential findings at necropsy were as follows: In the peritoneal cavity the abdominal organs were in their normal positions. The liver was asymmetric, the left lobe being bigger than the right lobe. The spleen was entirely absent. There was a common mesentery. In the chest a retrosternal abscess communicating with a subcutaneous abscess through a necrotic zone in the upper part of the sternum was found. The lungs were well aerated and not congested. The left lung was a mirror image of the right lung, there being a middle lobe. The trachea and bronchi were normal in appearance. The heart lay in the right hemithorax, but the apex pointed to the left. There was a left aortic arch with normal branching. The ductus arteriosus was obliterated. There was a purulent pericarditis. There were big septal defects between the two auricles and between the two ventricles. The right atrium was rudimentary. The right ventricle was not developed. The tricuspid valve was atretic. The pulmonary veins formed a common trunk that communicated with the superior vena cava and entered the right atrium. The pulmonary artery arose from the right ventricle. The superior vena cava communicated with the pulmonary vein in the right lung and with the innominate vein which entered the left atrium. The inferior vena cava entered the right atrium. The aorta arose from the left ventricle. The abdominal aorta descended normally on the left and the inferior vena cava on the right (Fig. 1). There was passive congestion of the abdominal organs.

Discussion

The post-mortem diagnoses of this case can be classified into two groups. On the one hand there were multiple congenital anomalies consisting of various malformations of the heart and agenesis of the spleen. On the other hand there were various manifestations of septicaemia. Whereas the signs and symptoms of septicaemia were readily recognized during life, the symptoms and signs of the heart anomalies were partly misinterpreted and diagnosed only at necropsy.

The occurrence of septicaemia in this case as well as the lack of response to adequate quantities of broad-spectrum antibiotics deserve special attention. A review of the pertinent literature seems to indicate that in many of the reported cases very severe purulent infections have occurred. Thus Ivemark (1955) found in eight of his 14 patients signs of purulent infections at post-mortem examinations.

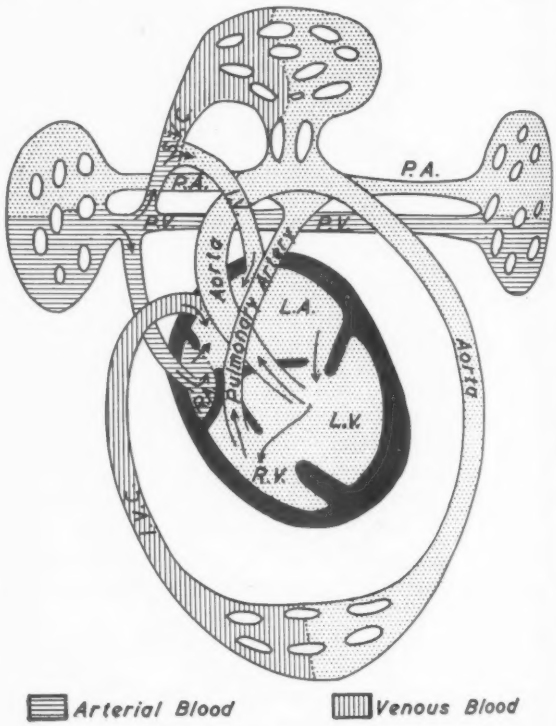

FIG. 1.—Diagrammatic picture of the heart and great vessels in a case with associated absence of the spleen.

R.V. = right ventricle
R.A. = right auricle
L.V. = left ventricle
L.A. = left auricle
I.V. = innominate vein
P.A. = pulmonary artery
P.V. = pulmonary vein
S.V.C. = superior vena cava
I.V.C. = inferior vena cava

Other cases of congenital absence of the spleen showing evidence of severe purulent infection at the time of death have been reported by Polhemus and Schafer (1952), Gardère (1908), McLean and Craig (1922), Feldmann (1930) and Leikin (1951). Ramsay (1850) reported a case of persistent gastro-enteritis of 12 months' duration in which at necropsy no spleen was found.

It seems, moreover, that not only does congenital absence of the spleen apparently predispose these young infants to infection, but surgical removal of the spleen in young infants is also accompanied by the same risk. Thus King and Shumacker (1952) pointed out that after splenectomy in infants under the age of 6 months septicaemia very frequently develops. Gellis (1954) reported three cases in which septicaemia developed several months after splenectomy. Hoefnagel (1956) reported two cases of repeated severe infections which ultimately led to their death in two brothers whose spleens were removed for idiopathic thrombocytopenic purpura.

An explanation of this relationship of purulent infection to the absence of the spleen is at present still conjectural. However, there is ample experimental evidence available to suggest that the spleen has a definite role in the defence mechanism of the body, probably through antibody formation. Thus in rodents removal of the spleen interferes with the development of an immune response (Rowley, 1950a). The same author has also demonstrated, in human beings who have undergone splenectomy, a failure to respond with a significant rise in antibody titre after the administration of an antigen (Rowley, 1950b). Jacobson and Robson (1952) have shown that shielding with lead the spleen in rabbits during total body irradiation prevents the usual reduction in these circumstances of circulating antibody concentration.

On the basis of the above evidence it seems fair to conclude that, unlike conditions in adults, the spleen of young infants plays a major role in the defence of the body against infection while other defence organisms at this age are apparently underdeveloped. This would explain the fact emphasized by King and Shumacker (1952) that patients whose spleen has been removed before the age of 6 months are relatively more prone to infection than older children undergoing splenectomy.

Serious infections in a cyanotic infant, even without clear-cut evidence of heart disease, should, therefore, serve as indications for the search for co-existent asplenia. When such a combination of cyanosis and persistent infections is observed, further studies should be performed. The chief aid in the diagnosis of this condition is derived from haematological examinations. A persistently increased number of Heinz bodies in the erythrocytes of the peripheral blood has been pointed out by Gasser and Willi (1952) as a constant feature in this syndrome. Bush and Ainger (1955) performed detailed studies in a case later proved to be one of agenesis of the spleen. They found that after the intravenous administration of twice the amount of iron necessary to increase haemoglobin to 18 g. target cells persisted, Howell-Jolly bodies were present throughout the clinical course, normoblasts that were present before the iron treatment increased sixfold after it, siderocytes appeared immediately after therapy and persisted and the leucocyte count was elevated throughout the clinical observation without cause. The osmotic fragility of the red blood cells was decreased.

It must be borne in mind, however, that the appearance of Heinz bodies or Howell-Jolly bodies does not in itself constitute conclusive evidence of asplenia. Gasser (1954) reported a Heinz body anaemia after topical application of 'resorcinol' in a case of infantile eczema. Heinz bodies are also found after the administration of methylene blue as well as in certain haemolytic anaemias. A full haematological examination, similar to the one performed by Bush and Ainger (1955) is, therefore, indicated in cases of suspected asplenia in order to reach an ante-mortem diagnosis.

Summary

A case of congenital absence of the spleen with associated multiple anomalies of the heart and the great vessels presented various manifestations of severe septicaemia unresponsive to adequate quantities of antibiotics. A review of the pertinent literature seems to indicate that a causal relationship exists between the agenesis of the spleen and the very severe infections observed in these cases. It is suggested that serious infections in a cyanotic infant, even without clear-cut evidence of heart disease, should lead to a search for co-existent asplenia.

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References

Bush, J. A. and Ainger, L. E. (1955). *Pediatrics*, **15**, 93.
Feldmann, B. A. (1930). *Jb. Kinderheilk.*, **129**, 221.
Garcère (1908). *Lyon méd.*, **110**, 897. Cited by Ivemark, B. I. (1955).

Gasser, C. (1954). *Helv. paediat. Acta*, **9**, 285.
—— and Willi, H. (1952). *Ibid.*, **7**, 369.
Gellis, S. S. (1954). *Year Book of Pediatrics*, 1954-55, Editor's comment, p. 275.
Hoefnagel, R. (1956). *Clin. Proc. Child. Hosp.* (*Wash.*), **12**, 48.
Ivemark, B. I. (1955). *Acta paediatr.* (*Uppsala*), **44**, suppl. 104.
Jacobson, L. O. and Robson, M. J. (1952). *J. Lab. clin. Med.*, **39**, 169.
King, H. and Shumacker, H. B., Jr. (1952). *Ann. Surg.*, **136**, 239.
Leikin, S. L. (1951). *Clin. Proc. Child. Hosp.* (*Wash.*), **7**, 236.
Martin, G. (1826). *Bull. Soc. anat. Paris*, **1**, 39. Cited by Ivemark, B. I. (1955).
McLean, S. and Craig, H. R. (1922). *Amer. J. med. Sci.*, **164**, 703. Cited by Ivemark, B. I. (1955).
Polhemus, D. W. and Schafer, W. B. (1952). *Pediatrics*, **9**, 696.
Putschar, W. (1934). In *Die Morphologie der Missbildungen des Menschen und der Tiere*, ed. Schwalbe, E., teil 3, abt. 3, pp. 759-856. Fischer, Jena. Cited by Ivemark, B. I. (1955).
Ramsay, H. A. (1850). *Charleston med. J. Rev.*, **5**, 728.
Rowley, D. A. (1950a). *J. Immunol.*, **64**, 289.
—— (1950b). *Ibid.*, **65**, 515.

DUPLICATION OF THE PITUITARY AND STOMATODAEAL STRUCTURES IN A 38-WEEK MALE INFANT

BY

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Duplication of the pituitary (hypophysis) and other structures in the region of the mouth may be regarded as a minor degree of partial twinning which did not go on to frank monster formation. Ahlfeld (1880), who considered that the first grade of duplication of the anterior end of the body was a doubling of the hypophysis, reports one case in man; and McCall (1943) records a double Rathke's pouch with two corresponding diencephalic diverticula in a 10-mm. C.R. rat embryo. No other reports of such duplications have been found in a search of the literature. These abnormalities are interesting not only because of their rarity, but also because they illustrate that twin formation may well occur, as postulated by Corner (1955), during the differentiation of the germ disc from the inner cell mass.

History

A 38-week male infant, born on March 11, 1956, of a primigravida aged 28 years, was sent to hospital on account of a double cleft palate and other malformations of the interior of the mouth. He died three days after birth and a full anatomical examination of the body was carried out after perfusion through the femoral arteries.

There was no history of congenital malformations in either the mother's or the father's family. The mother gave no history of any illness from early childhood, and had no pyrexial upsets during the pregnancy. Her menstrual periods were 'normal and regular'. Her last menstrual period had been on June 16, 1955. Slight uterine bleeding lasting 36 hours was noted on June 30, and a continuous loss lasting 21 days started on July 14, 1955.

General Description

The external appearance of the child was normal except that the mouth was wide, the lower lip was duplicated and the chin showed a central supernumerary prominence (Fig. 1). Inside the mouth two frenula, one on either side of the mid-line, connected the upper lip to the gum (Fig. 2). Two supernumerary central incisor teeth were contained in the gum between the frenula. Two mandibles, each with a distinct symphysis, were present (Fig. 3). The medial parts of these bones ended in a firm bar of tissue connecting the floor to the roof of the mouth. It was covered by squamous epithelium from which numerous racemose glands arose, and in the upper part consisted of large masses of striped muscle and some blood vessels. The vessels ran upwards through a gap in the sphenoid to the interior of the skull. A tongue lay within each mandibular arch, the left being the broader and more horizontal of the two. Posteriorly they were united to form a single broad lingual mass on which a single row of circumvallate papillae was present (Fig. 4). The muscles of the tongues and lower jaws, attached to the broad hyoid bone, could not be readily identified, but the right hypoglossal nerve supplied musculature in both tongues, while the left only supplied that on the left side.

A complete bilateral cleft palate was present, the clefts running backwards from behind the alveolus, and the oral and nasal cavities communicated freely with each other. A soft, whitish mass covered with fine hairs hung down from the nasal septum posterior to the alveolar arch. A second polypoid mass, almost completely obstructing the nasopharynx, hung down from the roof of the mouth behind and to the left of the upper attachment of the abnormal bar of tissue; it separated the uvular ends of the right and left palatal processes (Fig. 2). A tuft of long black hairs protruded downwards between this second mass and the abnormal bar. The upper border of the epiglottis was slightly notched, but no other evidence of duplication was found in the larynx, trachea, oesophagus, thoracic or abdominal viscera, or in the limbs.

FIG. 1.

FIG. 2.

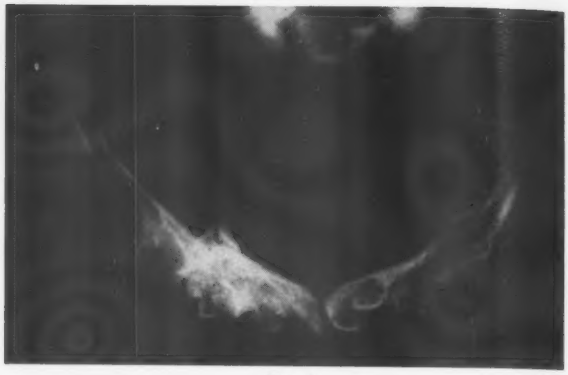

FIG. 3.

FIG. 4.

FIG. 1.—View of the mouth showing the right tongue, the abnormal bar with the alveolar margins, the double lip and the midline chin prominence.

FIG. 2.—The roof of the mouth. Two frenula join the upper lip to the gum, behind which lies a hair-covered polyp. Long hairs lie to the left of the cut end of the abnormal bar, and a polyp, covered with squamous epithelium, separates the uvular ends of the palate posteriorly. ×1·1.

FIG. 3.—Radiograph of the lower jaw. A well-marked symphysis separates the left half mandible from the medial mass of bone. A second symphysis can also be seen to the right of the midline.

FIG. 4.—The floor of the mouth. The double lower lips and lower alveolar ridges can be seen anterior to the two tongues. The cut lower end of the abnormal bar lies immediately anterior to the fused posterior lingual mass. ×1·6.

FIG. 5.

FIG. 6.

FIG. 7.

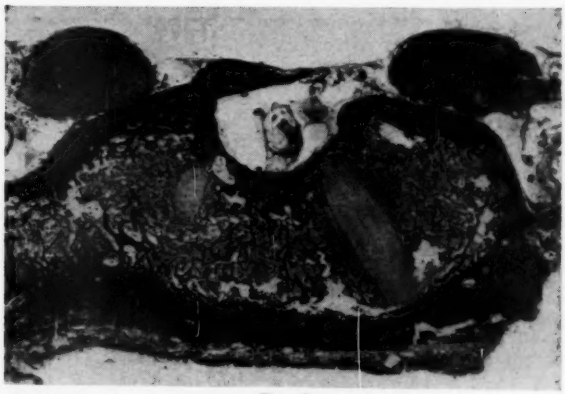

FIG. 8.

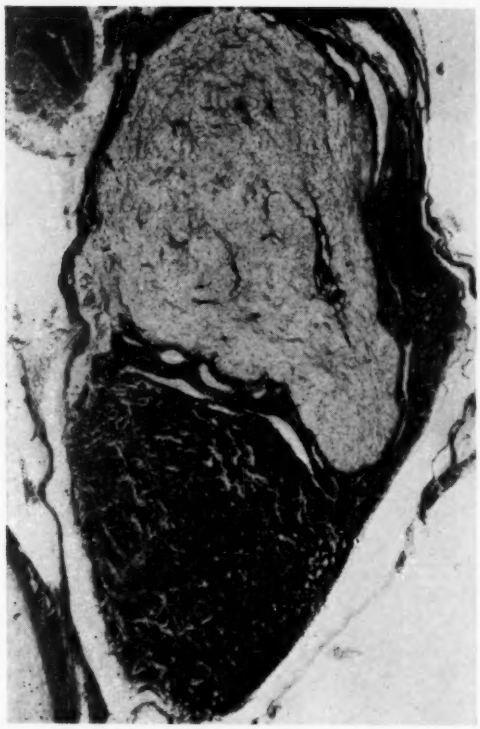

FIG. 9.

FIG. 5.—Base of the skull from above. The two hypophyses lie behind the optic nerves and internal carotid arteries. The depression antero-medial to the glands is referred to in Fig. 7. ×0·9.

FIG. 6.—The base of the skull in a normal full-term male infant to show the relations of the hypophysis. ×0·9.

FIG. 7.—Radiograph of the base of the skull after removal of the brain. The midline bony defect in the sellar region corresponds to the depression between the two hypophyses and transmitted blood vessels from the upper end of the abnormal bar to the interior of the skull.

FIG. 8.—Coronal section through the sellar region. The pars anterior of each pituitary lies laterally and blood vessels lie in a midline vacuity. Bars of cartilage subdivide the bone in an unusual manner. Ciliated columnar epithelium lines the pharynx in this region. ×3·7.

FIG. 9.—Low-power view of the left hypophysis showing the neural lobe, pars intermedia, cleft and the pars anterior. ×30.

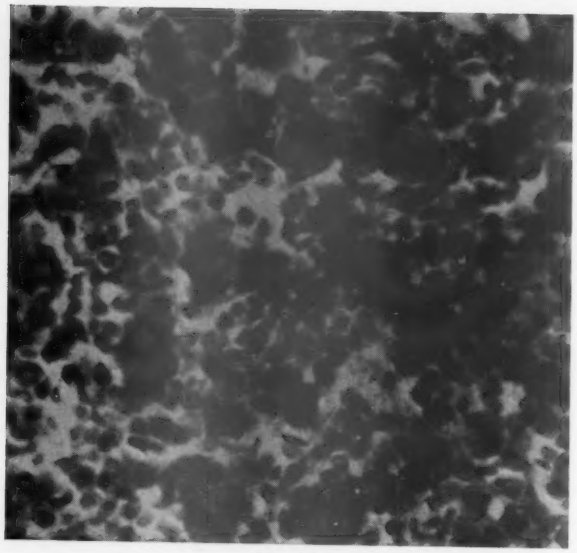

FIG. 10.

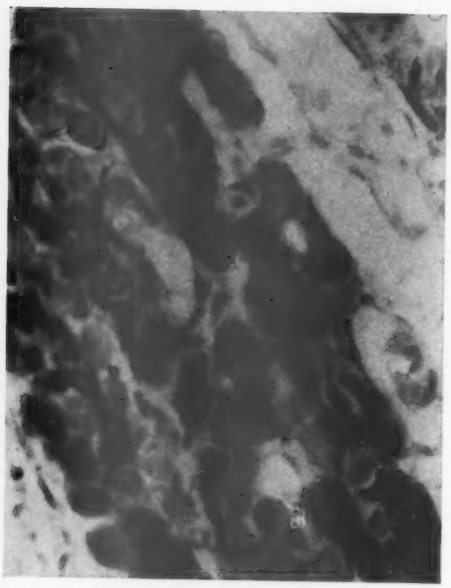

FIG. 11.

FIG. 10.—High-power view of the pars anterior. Blood-filled capillaries show as light areas. ×440.

FIG. 11.—High-power view of a portion of the rignt pharyngeal hypophysis. The cells are not so tightly packed as in the main glands. ×440.

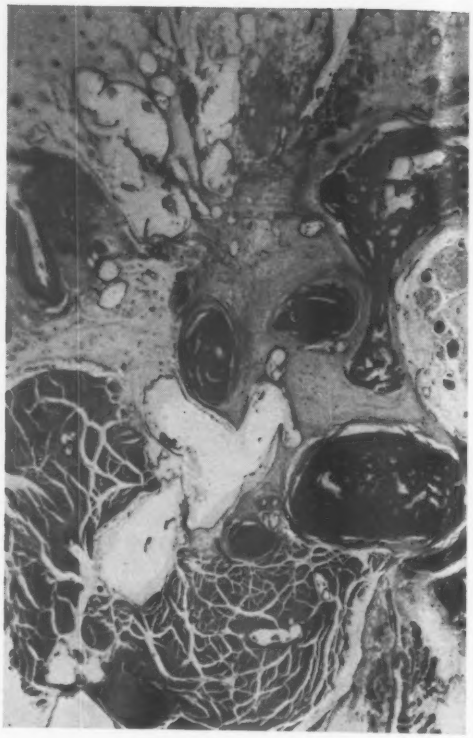

FIG. 12.

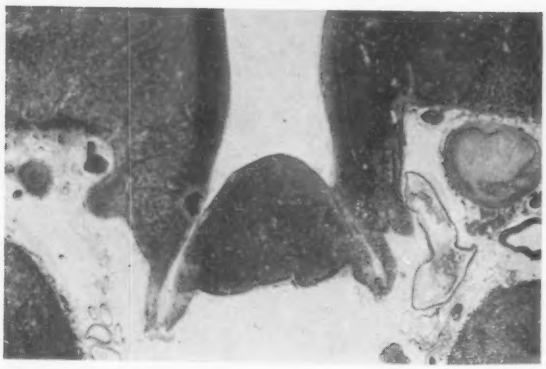

FIG. 13.

FIG. 12.—The upper attachment of the abnormal bar of tissue. Striped muscle covered by a squamous epithelium forms the bulk of this bar to the left of which is a mucoid polyp. The numerous mucous glands lie beside the adeno-hypophyseal tissue which is attached to the columnar epithelium in the depths of the laterally-placed crypts. ×7·25.

FIG. 13.—Coronal section of the brain. The two hollow hypophyseal stalks are separated by an elevation in the floor of the third ventricle, which contains numerous nerve cells. ×3·7.

Base of the Skull. The outstanding feature of the interior of the skull was the presence of two pituitary glands lying on either side of the midline postero-medial to the upturned ends of the internal carotid arteries (Figs. 5 and 6). Antero-medial to the glands there was a slight depression which corresponded in position to the absence of bone as seen on a radiograph (Fig. 7). Each hypophysis measured approximately 5 mm. in both antero-posterior and transverse diameters, and from 4 to 4·5 mm. vertically. They were more ovoid in coronal section and without the broad base seen in the hypophysis of a normal full-term male infant, which measured 6, 7 and 5 mm. in comparable diameters. The optic nerves were 17 mm. apart at the optic foramina as compared with 10 mm. in the normal, and the chiasma was correspondingly broadened.

Serial sections cut coronally at 10 microns were made of the base of the skull so as to include the whole of the hypophyses and the upper part of the naso-pharynx (Fig. 8). All the hypophyseal sections and every twelfth section anterior to that were mounted. Sections were stained with haematoxylin and eosin, pyrrol and eosin, Weigert and van Gieson stains, Mallory's or Masson's triple stains.

Histologically each hypophysis (Fig. 9) consisted of a neuro- and an adeno-hypophysis. The neural lobes, pars intermedia and clefts were small but otherwise normal. The adeno-hypophyses showed all the characters of normal glands both in vascularity, general arrangement of the cells and in their staining reactions (Fig. 10). Large accessory adeno-hypophyseal masses, presumably formed from the stems of Rathke's pouches, were found in the pharyngeal roof. These masses measured 1·4 mm. by 0·6 mm. on an average, and extended through 675 sections on the right side and 820 sections on the left side. They were composed of cells identical in appearance and staining reactions with those of the main adeno-hypophysis, and were equally vascular (Fig. 11). The mass on the left side was attached by a short diverticulum, and that on the right by a solid cord of cells to the epithelium of the pharynx. This epithelium was columnar at the points of attachment but became squamous and contained numerous hair follicles a short distance medial to these points (Fig. 12).

The Brain. The olfactory tracts were not present. Two hollow hypophyseal stalks projected downwards from the floor of the third ventricle behind the wide chiasma and anterior to two mammillary bodies. No other abnormalities were found in the brain. Coronal sections, at 10 microns, of the hypophyseal stalks and lateral walls of the third ventricle were made and stained for nerve fibres (Foot's modification of the Bielschowsky technique) and for cells (gentian violet stain). The floor of the third ventricle showed a median elevation separating two depressions which led down to the stalks (Fig. 13). Nerve cells were present in this elevation but no definite arrangement into nuclei could be made out. Normal supra-optic nuclei were present laterally. For comparison, the brain and hypophyseal region of a normal infant were also examined.

Discussion

Simple failure of union of embryonic masses around the stomatodaeum, such as led in Bosatra's (1955) case to a bifid tongue and median cleft in the upper lip, could not have caused the duplications described above. It is necessary, in order to explain them, to envisage a stage in early development during which a small deviation from the normal could occur which would influence the hypophyseal and oral regions and, by reason of the secondary chain of events initiated by it, bring about considerable changes in the head region. Duplication of cells of the prochordal plate and of the anterior end of the notochordal process at the fifteenth to sixteenth day of pregnancy would produce such changes, as it is these tissues which act on the overlying ectoderm inducing differentiation of the anterior end of the germ disc. Why duplication should have occurred, and the means whereby it was caused, are unknown, but, as Töndury (1955) states in his review of the problem of the developmental physiology of abnormal growth, physical and chemical factors must act at critical phases to produce abnormalities. Maternal ill health due to rubella is known to produce neural lesions, and avitaminosis (Ancel, 1954), hypervitaminosis (Giroud and Martinet, 1955) and other agents have been used experimentally in the production of foetal abnormalities (Fraser and Fainstat, 1951). No history of maternal ill health during the critical period of the pregnancy was discovered in this case, but the uterine bleeding, starting at about the fourteenth day of gestation and lasting 21 days, may well have a causal relationship.

A brief description of the normal development of the pituitary, based on the work of Gilbert (1935), will help in following the probable course of events leading to the production of the abnormalities.

The hypophysis develops, in the rat, from a proliferation of the undifferentiated ectoderm common to the neural plate and stomatodaeum, at the anterior end of the medullary groove. This ectoderm is situated just anterior to the stomatodaeal

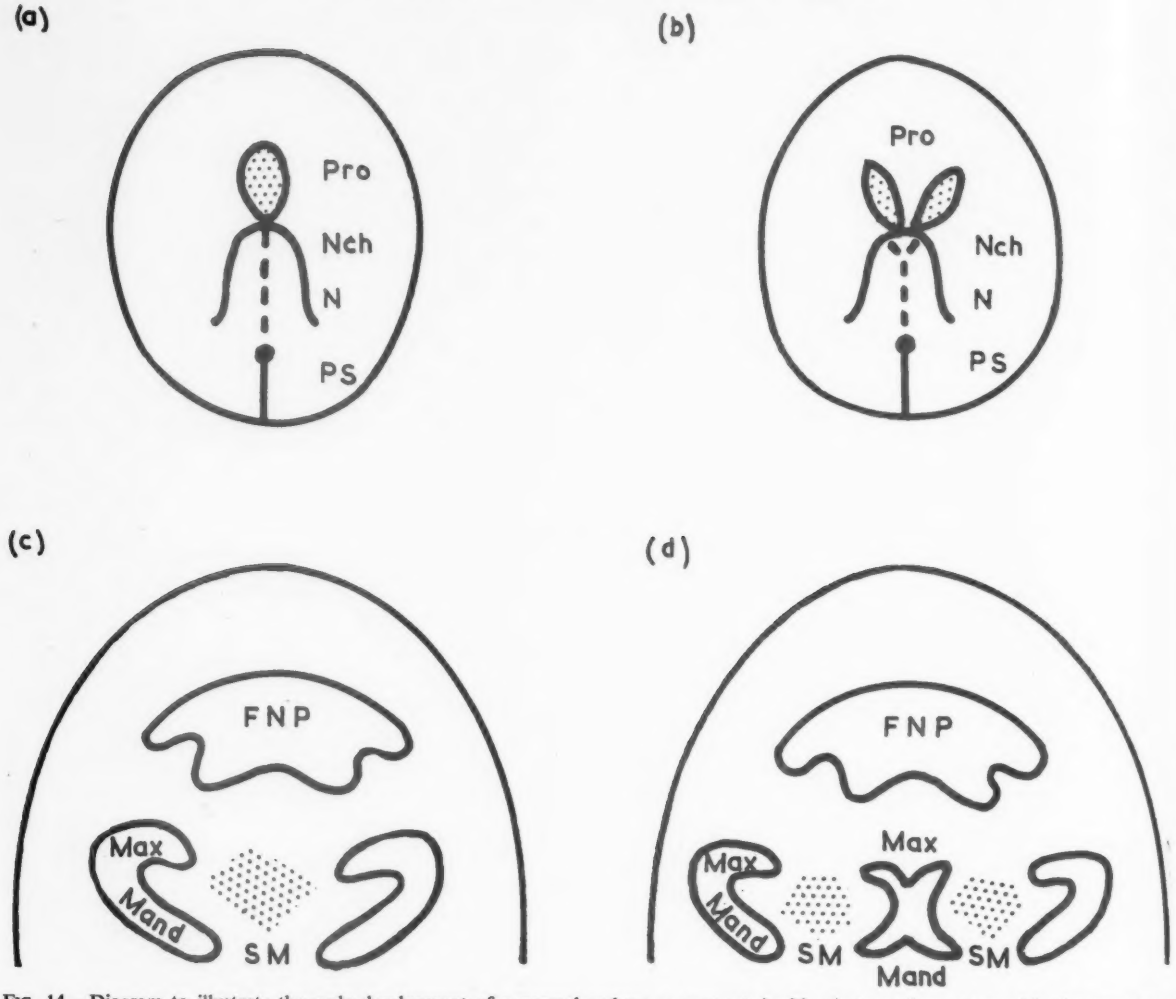

FIG. 14.—Diagram to illustrate the early development of a normal embryo as contrasted with what may have occurred in the present case. The embryonic shield is shown as if transparent and viewed from above in (*a*) and (*b*), and the stomatodaeal region as from in front and below in (*c*) and (*d*).

(*a*) The normal embryonic shield.
(*b*) Duplication of prochordal plate and anterior end of notochordal process.
(*c*) Normal mesoderm masses around the stomatodaeum.
(*d*) Duplication of mandibular and maxillary mesoderm between two stomatodaeal membranes.

Pro	=	Prochordal plate
N Ch	=	Notochordal process
N	=	Outline of presumptive neural tissue
P S	=	Primitive streak
F N P	=	Fronto-nasal process
Max	=	Maxillary swelling
Mand	=	Mandibular swelling
S M	=	Stomatodaeal membrane

(or oral) membrane and the notochord. The definitive neural and surface ectoderms form from this mass, and mesoderm then separates the neural tube from the surface ectoderm, except at the region of the developing hypophysis, where the initial apposition of ectoderms persists. Increase in the amount of this mesoderm produces the diverticulum known as Rathke's pouch. Specialized masses of mesoderm, from which the nose and upper and lower jaws are formed, develop into the fronto-nasal process above, and the mandibular and maxillary swellings on either side of the stomatodaeum.

In the present case the assumed duplication of the prochordal plate and anterior end of the notochord would presumably lead to duplication of the stomatodaeal region as a whole, and to two areas of persisting contact between neural and surface ectoderms, representing the anlagen of the two hypophyses. Mesoderm must then have surrounded and separated the two stomatodaeal areas from each

other, forming mandibular and maxillary swellings around each primitive oral opening, and a common fronto-nasal swelling above them (Fig. 14). In this way normal structures would form laterally, and duplicates, to the limits of the available mesoderm, would form medially.

Each medial maxillary swelling would then have produced alveolar tissue containing a single central incisor tooth, and a lip element, which, by fusion with the lateral elements, formed complete alveolar and labial arches with a double frenulum marking the lines of fusion. A single fronto-nasal process would produce the normal external nose, and fuse with all four maxillary processes to complete the upper lip. Internally the lower margin of the nasal septum must carry remnants of the medial maxillary swellings to the upper part of the medial mandibular processes, represented by the abnormal bar of tissue. Ectoderm has persisted along this margin, forming squamous epithelium and hair follicles, and may have prevented closure of the palate (Scott, 1955). Partial development of mandibular structures on the medial side of each primitive oral opening accounts for the double lower lip, two symphyses menti and two tongues, the single tongue posteriorly forming from medial and lateral elements.

Additional adeno-hypophyseal gland tissue in the pharyngeal roof is regarded by many writers as being a variant of the normal (Patten, 1946), and Boyd (1956) drew attention to the constancy of such tissue in human embryos and adults. The extent of this tissue in the present case and its similarity with the main adeno-hypophysis indicate that it may have been capable of functioning as a source of internal secretions. Its presence on both sides of the median bar of tissue is in keeping with the course of development outlined above.

It is evident then that the abnormal structures in this case can be explained as being secondary to a duplication of the organizers for the primitive mouth region. No proper explanation for the absence of the olfactory tract can be offered, unless it be assumed that the derangement of growth in the brain and nasal region was sufficient to prevent development of the olfactory bulbs.

Summary

Duplication of the hypophysis and parts of the upper and lower jaws of a 38-week male infant are described.

Considerable masses of adeno-hypophyseal tissue were found in the roof of the mouth in positions corresponding to the stem regions of two Rathke's pouches.

An embryological explanation of the likely chain of events leading up to the conditions observed at birth is offered. This postulates that a transitory duplication of the anterior end of the inductor system for the head region occurred at about the fifteenth to sixteenth day of pregnancy, and led to the production of two primitive oral openings around which relatively normal development took place.

I am indebted to Dr. Muriel Frazer of the Jubilee Hospital, Belfast, for the opportunity of examining this case both before and after death, to Dr. H. T. Sheils for the family and clinical history, to Professor J. J. Pritchard for his interest in the preparation of the paper, and to Mr. George Bryans for assistance with the photography and the preparation of the large number of microscopic slides involved.

References

Ahlfeld, F. (1880). *Die Missbildungen des Menschen*, pt. 1. Leipzig.
Ancel, P. (1954). *Arch. Anat. (Strasbourg)*, **37**, pt. 2, p. 1.
Bosatra, A. (1955). *Arch. ital. Otol.*, **66**, 416.
Boyd, J. D. (1956). *J. Anat. (Lond.)*, **90**, 595.
Corner, G. W. (1955). *Amer. J. Obstet. Gynec.*, **70**, 933.
Fraser, F. C. and Fainstat, T. D. (1951). *Amer. J. Dis. Child.*, **82**, 593.
Gilbert, M. S. (1935). *Anat. Rec.*, **62**, 337.
Giroud, A. and Martinet, M. (1955). VIe Congrès Fédératif International d'Anatomie. Paris.
McCall, J. O., Jr. (1943). *Anat. Rec.*, **87**, 215.
Patten, B. M. (1946). *Human Embryology*. Philadelphia.
Scott, J. H. (1955). *J. Anat. (Lond.)*, **89**, 561.
Töndury, G. (1955). *Münch. med. Wschr.*, **97**, 1009.

IDIOPATHIC HYPERLIPAEMIA

REPORT OF A CASE STUDIED WITH RADIOACTIVE IODINE-LABELLED FAT

BY

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The diagnosis of hyperlipaemia is made when the total serum lipids exceed 1 g./100 ml. (Holt, 1954). Hyperlipaemia may be associated with disorders of carbohydrate metabolism as in diabetes mellitus and von Gierke's disease; with liver damage due to hepatitis or poisoning with carbon tetrachloride, chloroform or phosphorus; with renal disease in 'nephrosis' and renal vein thrombosis; and with anoxia, anaemia, pancreatitis and hypothyroidism. A marked and persistent hyperlipaemia may be found unassociated with other conditions and is then known as idiopathic hyperlipaemia. Less than 50 cases of this type have been described in all age groups, but attention has been drawn to the condition by recent reports (Joyner, 1953; Gaskins, Scott and Kessler, 1953; Malmros, Swahn and Truedsson, 1954; *British Medical Journal*, 1954). A child with idiopathic hyperlipaemia is described below, together with studies with radioactive-iodine-labelled fat designed to try to find the cause of the abnormality.

Case Report

Alan, a 7-year-old boy, was admitted to the Children's Hospital, Sheffield, at the end of 1954. When younger he had had rubella, whooping cough and scarlet fever. Seven months before admission he had infective hepatitis. The illness began with nausea and anorexia. He became jaundiced and his stools were pale and his urine was dark. After a month's bed rest at home he apparently recovered completely.

During the previous two years he had had six attacks of vague central abdominal pain and fever. Each attack lasted about 24 hours and no cause had ever been found.

He was admitted to hospital on this occasion with acute tonsillitis. Penicillin was given and the tonsillitis rapidly subsided.

Examination showed Alan to be a well-developed boy of average intelligence. The liver was easily felt two fingerbreadths below the costal margin and it was smooth and firm but it was not tender. The spleen was also firm and extended an equal distance below the left costal margin. The optic fundi showed the typical picture of lipaemia retinalis (Fig. 1). Xanthomata were not found.

FIG. 1.

When blood was drawn for liver function tests the serum was noted to be like cream. The total serum lipids were 4 g./100 ml. The excess lipids were neutral fat. The serum cholesterol was 237 mg./100 ml. Foam cells formed 1·6% of the bone marrow.

The full blood count and urine analysis were normal. The serum bilirubin was 0·5 mg./100 ml., the alkaline phosphatase 6·8 units (Jenner and Kay) and the serum proteins were albumin 3·2 g. and globulin 4·0 g./100 ml. Radiography did not show intra-abdominal calcification and the subcutaneous tissues were of normal thickness.

Alan was thought by his parents to be the weakling of the family. His parents and sisters did not show

clinical evidence of hyperlipaemia and their serum lipids were:

Father	360 mg./100 ml.
Mother	540 mg./100 ml.
Sister (4 years)	730 mg./100 ml.
Sister (15 months)	670 mg./100 ml.

The hyperlipaemia persisted whilst Alan had a normal diet. The highest level of the serum lipids was 7·7 g. Within 48 hours of giving a diet containing less than 5 g. of fat a day the retinal vessels appeared normal and a day later the serum lipids had fallen to 1 g./100 ml. The size of the liver and spleen did not alter during a week on this very low fat diet nor did they change over the period of a year on a diet containing about 15 g. of fat per day.

Investigations with Radioactive Iodine (I^{131})-labelled Fat

The basis of the investigations performed lies in the fact that during the metabolism of radioactive iodine-labelled fat the iodine is liberated and appears in the urine and the thyroid gland. If the thyroid gland is 'blocked' by the previous administration of potassium iodide then the radioactive iodine appearing in the urine indicates the quantity of fat that has been metabolized. This method has been used in the Department of Pharmacology of Birmingham University (Pover, Frazer and Sammons, 1955).

Olive oil was iodinated with the isotope I^{131}. This iodinated oil was then incorporated into a quantity of butter fat as carrier. Two small portions of approximately 5 μc. of radioactive fat were weighed accurately on to rice paper. One portion was the test dose and was eaten on the rice paper. The other portion was dissolved in 50 ml. of a mixture of toluene, 3 parts, and chloroform, 1 part. A 1 in 100 dilution of this solution was made with the same solvent. The radioactivity of this standard solution was counted and from this the radioactivity of the dose given was calculated.

Alan had been receiving a consistent diet for at least five days before each test. The radioactivity of his urine was measured to ensure that there was no residual activity from previous tests. Four 0·1 g. doses of potassium iodide were given at equal intervals during the 24 hours before the test. At the start of each test a specimen of venous blood was drawn for the estimation of the serum lipids, the patient emptied his bladder, and then the test dose of fat was given on an empty stomach. Thereafter all the urine voided was collected for four days. The urine was preserved with toluene. The radioactivity of each 24-hour specimen of urine was counted, and the results, after correction for decay, were expressed as a percentage of the activity of the test dose.

Three tests were performed. In the first test the patient was on the normal ward diet, with a fat content of approximately 45 g. per day. The second test was with a diet containing not more than 5 g. of fat per day. In the third test the fat content of the diet was approximately 15 g. per day. Table 1 shows the weight and radioactivity of the test doses and standards, the fat content of the diets and the serum lipid levels at the start of each test.

TABLE 1

WEIGHT AND RADIOACTIVITY OF DOSES AND STANDARDS OF LABELLED FAT, FAT CONTENT OF PATIENT'S DIETS, AND SERUM LIPID LEVELS AT THE START OF EACH TEST

Test	Weight of Fat Used (mg.)	Radio-activity of Dose (μc.)	Approximate Fat Content of Patient's Diet (g./day)	Total Serum Lipids at Start of Test (g./100 ml.)
1	115	4·05	45	4·2
2	320	3·14	5	1·2
3	255	3·47	15	2·0
Standard for tests 1 and 2	103	3·63		
Standard for test 3	248	3·37		

Results

The results obtained are shown in Table 2. The results obtained by Sammons and Pover in a normal child using the same method are included for comparison. In the three tests upon the patient there is a similar pattern of excretion of radioactive iodine in the urine. Between 22% and 46% of the total dose was present in the urine within 24 hours and between 47% and 69% within 48 hours. Up to 10% of the total dose appeared in the third 24-hour period, but thereafter much smaller amounts were present. In tests 1 and 3 more than 75% of the test dose had appeared in the urine after 96 hours. In test 2 57% of the test dose had been detected after 96 hours. In the normal child 12% of the test dose was detected after 24 hours, 58% after 48 hours and 70% after 96 hours.

TABLE 2

APPEARANCE OF RADIOACTIVITY IN URINE AFTER DOSE OF RADIOACTIVE-IODINE (I^{131})-LABELLED OLIVE OIL

Test	Radioactivity in Urine (% of total dose given)				
	0–24 Hours	25–48 Hours	49–72 Hours	73–96 Hours	0–96 Hours
1	34·3	25·2 (59·5)	10·0	5·7	76·2
2	22·1	23·7 (46·8)	7·9	2·3	57·0
3	46·7	22·5 (69·2)	5·2	3·2	77·6
Normal child	12	46 (58)	9	3	70

Discussion

The cases of idiopathic hyperlipaemia in children that have been reported present a characteristic

clinical picture. Joyner (1953) has pointed out that the features are not as evident in the adult cases. There are often attacks of abdominal pain and fever. The liver and spleen are enlarged. The serum is milky and when the serum lipids exceed about 3·0 g./100 ml. the retinal vessels appear white (Davies, 1955). The patient reported showed all these features. In addition his parents looked upon him as the weakling of the family. This frailty may be part of the clinical picture in children, for it is mentioned in half the case reports (Opitz, 1935; Franklin and Avery, 1937; Holt, Aylward and Timbus, 1939; Bernstein, Williams, Hummel, Shepherd and Erickson, 1939; Goodman, Shuman and Goodman, 1940; and Harslöf, 1948).

The illness seven months before the patient was admitted to hospital was probably hepatitis. This probably did not cause the hyperlipaemia as such tests of liver function as the serum bilirubin, the alkaline phosphatase and the plasma proteins were normal. The flocculation tests of liver function were found to be unreliable in the presence of hyperlipaemia.

In the case reported there was no family history of hyperlipaemia, but it has been reported in other cases (Holt *et al.*, 1939; Levy, 1946; Bruton and Kanter, 1951; Movitt, Gerstl, Sherwood and Epstein, 1951; Gaskins *et al.*, 1953; Malmros *et al.*, 1954).

Aetiology

Holt *et al.* (1939) suggested that the attacks of abdominal pain and fever were due to the rapid accumulation of fat in the liver and spleen. In their patient the attacks occurred when the serum lipids exceeded 8 g./100 ml., and they were associated with further enlargement of the liver and spleen. This variation in the size of the liver and spleen was not seen in the present case but the lipids did not reach quite such high levels.

The liver biopsy studies of Koszalka and Levin (1950), Movitt *et al.* (1951), and Bruton and Kanter (1951), and the necropsy reports of Chapman and Kinney (1941) and Thannhauser (1950) showed that there may be a considerable accumulation of fat in the liver. The appearances suggested passive accumulation of fat rather than defective metabolism of fat by the liver.

One case of idiopathic hyperlipaemia has been reported by Goodman *et al.* (1940) in which there was an absence of lipase in the serum. This was not found in the cases reported by Bloomfield and Shenson (1947), Thannhauser (1950), Bruton and Kanter (1951) and Joyner (1953). The serum lipase was not estimated in the present case.

Holt *et al.* (1939) suggested that fat metabolism in their patient was normal because she had a normal respiratory quotient and when starved she developed ketosis promptly and normally. Thannhauser and Stanley (1949) carried out original experiments with radioactive iodine-labelled fat and maintained that idiopathic hyperlipaemia was due to a decreased utilization of fat by the tissues. Twelve adults were studied. Ten were normal and two had idiopathic hyperlipaemia. These patients were given olive oil tagged with radioactive iodine I^{131} and the radioactivity of the serum, urine and thyroid gland was measured. The total activity in the urine and thyroid gland was thought to represent the fat that had been metabolized. In all the patients the peak of activity in the serum was reached between three and six hours but in those with hyperlipaemia the peak level was two to five times higher than in the normal patients. The disappearance of activity from the serum was prolonged in the patients with hyperlipaemia as compared with the normal patients. The rate of metabolism of the labelled fat as measured by the I^{131} in the urine and thyroid gland was lower in those with hyperlipaemia than in the normal adults during the early hours of the test, which is the period covered by the graphs of the results. This result may have occurred because during this period the radioactive iodine was accumulating in the serum.

Hahn (1943) showed that alimentary lipaemia could be reduced or abolished by the injection of heparin. The agent in the serum following an injection of heparin which is responsible for this phenomenon has become known as the clearing factor. Engelberg (1955) has reviewed the knowledge of this factor. Absence of the clearing factor would give rise to hyperlipaemia, but Lever, Herbst and Lyons (1955) concluded that so far there was insufficient evidence to warrant the conclusion that this was the cause of idiopathic hyperlipaemia.

Present Investigation

Thannhauser and Stanley (1949) studied adults and employed larger doses of radioactive material and a technique different from the present investigation. It is not feasible, therefore, to compare their results with those obtained in this study. The results reported here suggest that delayed metabolism of fat was not the cause of the hyperlipaemia. As judged by these few results the general pattern of metabolism was similar in the patient and in the normal child. In tests 1 and 3 the proportion of the total dose of radioactivity appearing in the urine in the first 24 hours was considerably greater than in the normal child. There are too few observations to justify the conclusion that in these tests the meta-

bolism of fat was more rapid than in the normal child, but it would seem unlikely that there was delayed fat metabolism.

In test 2 less of the total dose of activity appeared in the urine than in either tests 1 and 3 or in the normal child. This test was done when the patient was taking an almost fat-free diet, and the serum lipids were relatively low. The result observed may have been due to an increased retention of fat in the serum in this instance.

These observations do not support the theory of Thannhauser (1950), but would be in accord with an absence of the clearing factor. Grossman (1954) has described how the clearing factor can be estimated in human plasma and it is hoped that it will soon be possible to study this factor in the patient reported.

Treatment

Both in this patient and in most of the other reported cases there was a prompt and appreciable fall of the serum lipids following a low-fat diet. Bruton and Kanter (1951) showed by liver biopsy studies on their patient that after a few days on a low-fat diet most of the fat accumulated in the liver had disappeared. It would seem to be reasonable, therefore, to prescribe a low-fat diet for these cases. This seems to relieve the attacks of abdominal pain. Ahrens (1954) has reported recent studies on the patient originally described by Holt *et al.* (1936). She had reached 29 years of age and enjoyed reasonably good health. The liver and spleen were not now enlarged and occasional attacks of abdominal pain were thought to be due to lapses in the low-fat diet. Malmros *et al.* (1954) and Lever, Herbst and Hurley (1955), however, have stated that atherosclerosis may be a serious long-term problem and they recommend the use of very strict diets. The patient reported here was able to tolerate a low-fat diet which kept him free from attacks of abdominal pain, but when the fat content was reduced further in an attempt to obtain normal serum lipid levels, he refused to keep to the diet. Lever, Herbst and Hurley (1955) have suggested that heparin should be used in conjunction with a low-fat diet to keep the serum lipid level as low as possible. An injection of heparin may be justified to hasten the lowering of the serum lipid level during an attack of abdominal pain. The routine use of this drug would probably not be tolerated, and, as heparin is a drug which is not free from hazards, such a course is probably not justified.

Holt *et al.* (1939) studied the action of lecithin, choline, thyroxin, insulin, lipocaic, anterior pituitary factor and liver extract but failed to observe any response. Gaskins *et al.* (1953) used cortisone and A.C.T.H. but the results were variable.

A moderately low-fat diet within the limits tolerated by the patient would seem a reasonable recommendation for these cases at the present time.

Summary

The case of a 7-year-old boy with idiopathic hyperlipaemia is recorded.

Studies with radioactive-iodine-labelled fat upon the patient are compared with similar studies on a normal child. There was no evidence of a delay in the metabolism of the labelled fat in the patient.

I wish to thank Professor R. S. Illingworth for permission to study this patient and for helpful advice and criticism.

I am especially grateful to Dr. H. G. Sammons and Dr. W. F. Pover of the Department of Pharmacology, Birmingham University, who gave me considerable advice and made available to me their results obtained in the study of a normal child. Dr. Pover prepared the radioactive-iodine-labelled fat.

Professor G. M. Wilson of the Department of Pharmacology and Therapeutics of Sheffield University, allowed me to use apparatus, and Dr. G. Tudhope of the same Department gave valuable help in the tests for excretion of radioactive urine.

Acknowledgements are also due to the University of Sheffield Research Fund for a grant for this study.

I also wish to thank Mr. A. B. Nutt, F.R.C.S., for his help in this case.

References

Ahrens, E. H. (1954). 11th M. & R. Pediatric Research Conference, p. 30. Columbus, Ohio.

Bernstein, S. S., Williams, H. H., Hummel, F. C., Shepherd, M. L. and Erickson, B. N. (1939). *J. Pediat.*, **14**, 570.

Bloomfield, A. L. and Shenson, B. (1947). *Stanford med. Bull.*, **5**, 185.

British Medical Journal (1954), **2**, 1096.

Bruton, O. C. and Kanter, A. J. (1951). *Amer. J. Dis. Child.*, **82**, 153.

Chapman, F. D. and Kinney, T. D. (1941). *Ibid.*, **62**, 1014.

Davies, W. S. (1955). *A.M.A. Arch. Ophthal.*, **53**, 105.

Engelberg, H. (1955). *Amer. J. Physiol.*, **181**, 309.

Franklin, S. M. and Avery, H. (1937). *Proc. roy. Soc. Med.*, **30**, 711.

Gaskins, A. L., Scott, R. B. and Kessler, A. D. (1953). *Pediatrics*, **11**, 480.

Goodman, M., Shuman, H. and Goodman, S. (1940). *J. Pediat.*, **16**, 596.

Grossman, M. I. (1954). *J. Lab. clin. Med.*, **43**, 445.

Hahn, P. F. (1943). *Science*, **98**, 19.

Harslöf, E. (1948). *Acta med. scand.*, **130**, 140.

Holt, L. E. (1954). 11th M. & R. Pediatric Research Conference, p. 28. Columbus, Ohio.

——, Aylward, F. X. and Timbus, H. G. (1936). *J. clin. Invest.*, **15**, 451.

——, ——, —— (1939). *Bull. Johns Hopk. Hosp.*, **64**, 279.

Joyner, C. R. (1953). *Ann. intern. Med.*, **38**, 759.

Koszalka, M. F. and Levin, J. J. (1950). *Ibid.*, **33**, 473.

Lever, W. F., Herbst, F. S. M. and Hurley, N. A. (1955). *A.M.A. Arch. Derm.*, **71**, 150.

——, —— and Lyons, M. E. (1955). *Ibid.*, **71**, 158.

Levy, B. M. (1946). *J. Pediat.*, **29**, 367.

Malmros, H., Swahn, B. and Truedsson, E. (1954). *Acta med. scand.*, **149**, 91.

Movitt, E. R., Gerstl, B., Sherwood, F. and Epstein, C. C. (1951). *Arch. intern. Med.*, **87**, 79.

Opitz, H. (1935). *Dtsch. med. Wschr.*, **61**, 88.

Pover, W. F., Frazer, A. C. and Sammons, H. G. (1955). Résumé of Communications at the Third International Congress of Biochemistry at Brussels, No. 13/37, p. 119.

Thannhauser, S. J. (1950). "Lipidoses." (Reprinted from *Oxford Loose-Leaf Medicine*.) New York.

—— and Stanley, M. M. (1949). *Trans. Ass. Amer. Phys.*, **62**, 245.

SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN WITH CALCIFICATION OF THE TISSUES

BY

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(RECEIVED FOR PUBLICATION OCTOBER 14, 1956)

The following case is of interest as it presents some features of subcutaneous fat necrosis not previously described. Calcification of the tissues was seen radiologically and a raised serum calcium level caused symptoms similar to those of idiopathic hypercalcaemia.

Case Report

A girl weighing 7 lb. 14 oz. was born at the Elsie Inglis Memorial Hospital in August, 1953. The child was a breech presentation with extended legs and after a long, inert labour of 66 hours was born by breech extraction.

The mother was 38 and this baby was her first after 15 years of marriage. There had been two previous miscarriages. This baby also nearly miscarried at eight weeks and her mother had to rest in bed for one month at that time. Otherwise the pregnancy progressed satisfactorily. The pelvic measurements were normal.

At birth the baby was limp and a poor colour for several days. She had petechial haemorrhages over the face and bilateral subconjunctival haemorrhages. She was rather irritable and had a shrill cry which settled with sedatives.

On the second day after birth she developed marked oedema of the limbs and trunk which did not pit on pressure, the skin being tightly stretched.

On the fifth day after birth, sharply defined areas of subcutaneous induration could be felt in the back, shoulders and thighs, and the overlying skin was bluish red.

On the ninth day the swelling in the left thigh became soft and fluctuant and thick, brownish-yellow fluid was aspirated and sent for culture, and on the following day the 'abscess' had to be opened. Both these specimens were reported sterile.

During this time the general condition of the baby was good. She was hungry, gained weight and had no temperature.

A few days later another area of softening developed in the thigh and other indurated lumps appeared in the other thigh, anterior chest wall and groin and both buttocks became very hard, the skin over them being hot, red and angry. Except on the buttocks the skin over the new lesions was not red. The lumps were now discrete, indurated areas freely movable over muscle and not attached to the skin.

When 1 month old the temperature was raised for the first time and from this moment the baby became listless and reluctant to take her feeds and she failed to gain weight. She also started to vomit after feeds. She was not breast fed.

Haemoglobin was 120%, leucocytes 10,300 (eosinophils 3%, neutrophils 30%, lymphocytes 62%, monocytes 3%).

The urine contained albumin and granular casts and was acid, previously having been normal and alkaline.

The temperature swung from 101° to 103° F., but several blood cultures were sterile.

Radiographs showed some fuzziness in the subcutaneous tissues just where the areas of induration were to be felt.

Biopsy of a nodule led to the diagnosis of fat necrosis with calcification.

Pathological Report. The pathological report was as follows:

> MACROSCOPICAL FEATURES. The specimen is a small piece of skin with subjacent subcutaneous fatty tissue. In the latter is a rather ill-defined indurated mass, part of which has a whitish appearance.
>
> MICROSCOPICAL REPORT. The epidermis and dermis are healthy. The whitish subcutaneous nodule appears in the section as a small cavity in the fatty tissue filled with structureless necrotic debris and lumps of calcareous material. The wall of this cavity is formed by a layer of fibrous granulation tissue showing a vigorous foreign body reaction. Many of the giant cells contain acicular spaces that have been occupied by crystals, probably of cholesterin. This foreign body reaction extends to some distance from the cavity, along the fibrous septa between the fat lobules. The fatty tissue in these places shows necrotic changes: the fat cells are large, the cell membranes are ill-defined and stain bluish and most of the nuclei have disappeared. Small calcified particles occur in many of these areas. Only in one small area is there some infiltration by polymorph leucocytes; this is at some distance from the cavity, and is a relatively sparse infiltration, not an abscess.
>
> INFERENCE. At the stage now reached by the lesion it is impossible to tell what it was in the beginning. The foreign body reaction appears to have been evoked by fat necrosis, and the calcification to have occurred in necrotic fat. There is

extremely little to suggest a pyogenic infection, which, if present initially, must have died out some time ago.

(Sgd.) A. R. MACGREGOR.

Another radiograph taken when the baby was 7 weeks old showed definite calcification in the subcutaneous tissues (Fig. 1).

FIG. 1.

The serum calcium level estimated at this time was 12 mg. %.

The baby was kept in hospital until she was 2½ months old as her temperature remained high, rising to 103-104° F. and was not affected by any antibiotics, although a wide variety were tried.

There were remissions when the temperature remained at 99° F., but these were not due to the treatment.

Her general condition, however, was quite good; she was gaining weight slowly and was quite lively, so she was sent home.

Unfortunately we were unable to see her again until she was 7 months old. At this time she weighed only 11 lb. 7 oz., was frequently sick and was only gaining about 2 oz. a week. She had no appetite, her muscle tone was poor but she was no longer running a temperature. However, she was bright and lively and had a high colour. There were a few lumps to be felt now although there was considerable fibrosis beneath the scars where the two incisions had been made. She was not able to sit up and the anterior fontanelle was nearly closed.

The serum calcium level was 13·9 mg. %. The results of other investigations are tabulated.

Calcification of the tissues seen radiologically was substantially the same.

Her vitamin D intake was stopped.

The urine was acid (S.G. 1001).

Progress continued to be very slow indeed due to continued vomiting so she was readmitted to hospital when she was 10 months old and put on a low-calcium diet (serum calcium content, 13·3 mg. %), but her weight decreased on this régime and it was therefore discontinued.

Results of investigations at the time were substantially the same. The blood urea nitrogen and serum calcium levels were still raised. Radiographs showed that the calcification in the tissues was diminishing.

She started to make progress while in hospital, vomiting ceased and the weight increased.

She was seen again when 1 year old (weight, 20 lb.); she had just sat up without support. She had eight teeth and the anterior fontanelle was practically closed. At no stage was a systolic murmur heard as noted by some workers.

At 15 months she was eating much better, not vomiting at all and gaining 4 oz. a week; she was lively and muscle tone was good.

A radiograph showed that calcification in the soft tissues had now practically disappeared and only traces were still apparent in the right buttock. The serum calcium was now normal but the B.U.N. was still raised. Another radiograph taken when she was 2 years old was normal.

Discussion

Very few cases of subcutaneous fat necrosis have been reported where calcification in the tissues has been demonstrated radiologically.

Harrison and McNee (1926) reported two cases with calcification shown radiologically; one of these children died, but the other recovered. In the fatal case the serum calcium level during the illness was

TABLE

RESULTS OF INVESTIGATIONS AT DIFFERENT AGES

	7 Weeks	10 Weeks	7 Months	10 Months	15 Months	2 Years
Serum calcium (mg. %)	12	10·3	13·9	13·3	9	10
			repeated			
Inorganic phosphorus (%)		3·5	4·2	4·4		
Serum cholesterol (mg. %)		127		170		
chlorides (mg. %)			660	570	540	
CO_2-combining power (Vol. %)			67·5			
Total protein (mg. %)			6·9		6·4	
Blood urea nitrogen (mg. %)			30	32	27	16
Hb (%)		95	70	80		

9·3 mg./100 ml. In the other the serum calcium level was 15 mg. at 6 months of age, at 9 months 11·8 mg., while calcification seen in the radiograph persisted but diminished in amount over a few months.

Morse (1921) reported a child showing calcification radiologically at 3½ years, but did no follow up.

Bernheim-Karrer (1933) described 15 cases of subcutaneous fat necrosis and only one is mentioned as showing calcification in a radiograph taken at 4 weeks of age: this had disappeared by 7½ months.

The latter authors do not record the serum calcium levels in their cases. Clay (1956) reported a case of extensive subcutaneous fat necrosis with massive calcification, in which there was also found a high serum calcium level associated with symptoms of hypercalcaemia.

The case now being reported is similar to Clay's case and also had symptoms of idiopathic hypercalcaemia similar to those described by Payne (1952) and Lightwood (1952), and later Creery (1953) and Lowe, Henderson, Park and McGreal (1954). Like their cases our patient failed to thrive, had anorexia and vomiting associated with wasting, hypotonia and a pink complexion, though without constipation of any degree.

She recovered as soon as the calcium in the subcutaneous tissues disappeared and the serum calcium became normal. As would be expected the recovery was gradual, but she was behaving quite normally at 15 months when the radiographs showed only faint traces of calcium and the serum calcium level was now only 9 mg. %.

No mention is made in the earlier reported cases of the occurrence of the now known symptoms of idiopathic hypercalcaemia following subcutaneous fat necrosis with calcification in early infancy, but many of these cases died in the early stages of the disease.

Summary

A case of a baby with subcutaneous fat necrosis is described with the unusual features of prolonged calcification of the tissues demonstrable by radiographs and lasting for 15 months. This condition was associated with raised serum calcium levels. While the serum calcium level was raised the patient had symptoms similar to those of idiopathic hypercalcaemia. The symptoms regressed as the calcification disappeared from the tissues and the blood calcium became normal.

References

Bernheim-Karrer, J. (1933). *Z. Kinderheilk.*, **55**, 695.
Clay, P. R. (1956). *Proc. roy. Soc. Med.*, **49**, 598.
Creery, R. D. G. (1953). *Lancet*, **2**, 17.
Harrison, G. A. and McNee, J. W. (1926). *Archives of Disease in Childhood*, **1**, 63.
Lightwood, R. (1952). *Ibid.*, **27**, 302.
Lowe, K. G., Henderson, J. L., Park, W. W. and McGreal, D. A. (1954). *Lancet*, **2**, 101.
Payne, W. W. (1952). *Archives of Disease in Childhood*, **27**, 302.

RADIOLOGICAL CALCIFICATION OF INTERVERTEBRAL DISCS IN CHILDREN

BY

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It seems strange that a child should develop calcification of the intervertebral discs, a process which is generally regarded as degenerative in nature, but such is the case in the rare disorder first described by Báron in 1924. There are only 16 cases of this condition in children described in the literature, the most complete description being that of Silverman (1954) who reported seven cases and considered that it was more common than the number of reported cases would suggest.

Calcification of intervertebral discs has been recognized in association with certain metabolic disturbances, particularly alkaptonuria, but in this disease the process is generalized throughout the spine, whereas in the type referred to above it is localized to a maximum of four segments.

The process may affect either the nucleus pulposus or the annulus fibrosus, but the latter is the more common in children. The cervical and thoracic portion of the spine is more frequently affected than the lumbar region.

Symptoms referable to the affected area may or may not be present, but do not appear to bear a close relationship to the development or disappearance of the calcium deposits. Occasionally the lesion has been detected in a routine chest radiograph. Calcification in the cervical region is more likely to be associated with symptoms than when the thoracic or lumbar region is involved.

The symptoms are backache, stiffness of the spine, and occasionally torticollis. Associated congenital abnormalities have been noted in three of the 16 recorded cases but the relationship between the two is not clear. The following case belongs to the group with local symptoms.

Case History

C.Z., a 5-year-old child, born of Dutch parents, developed some stiffness and pain in the upper part of the back on March 20, 1956. These symptoms were most noticeable in the mornings and tended to improve throughout the day. However, over the next two weeks the stiffness became more marked and the pain more severe and she was admitted to hospital on April 16. There were no other symptoms and she had not been febrile.

Examination on admission showed a healthy looking child, with a normal temperature, crying with pain in her back. She was unable to sit up without assistance and there was marked neck and back stiffness. There was slight tenderness in the upper thoracic spine, but no deformity. All other systems were normal and there were no congenital abnormalities.

The white count was 14,000 of which 60% were polymorphonuclear leucocytes. The sedimentation rate was 10 millimetres in the first hour and the Mantoux test was negative. A radiograph of the spine showed well marked calcification of the intervertebral discs between

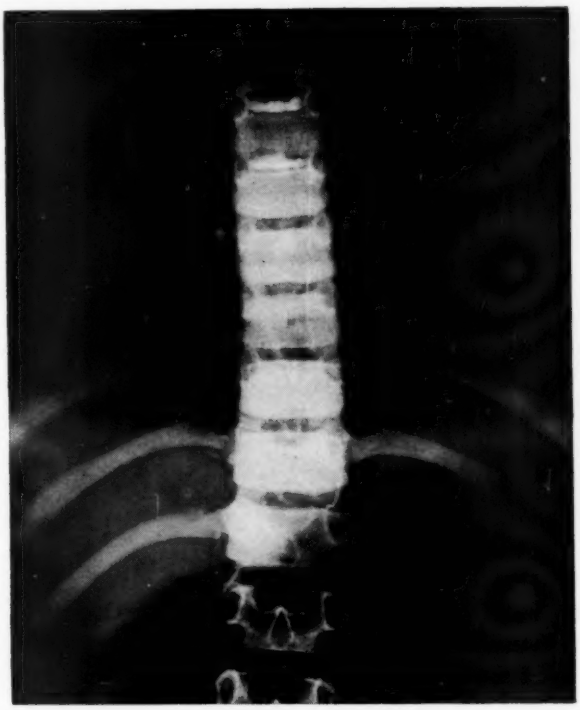

FIG. 1.

FIG. 2.

the fourth, fifth and sixth thoracic vertebrae (Figs. 1 and 2). No calcification was seen elsewhere. No homogentisic acid was detected in the urine. Calcium and phosphorus estimations were not carried out.

The pain and back stiffness remained marked for three days. Over the succeeding week the symptoms gradually subsided and 10 days after admission she appeared perfectly well and had a completely mobile spine. On August 13 the radiological appearances in the vertebrae were unchanged.

Discussion

There appears little doubt that there is a relationship between the pain and back stiffness and the radiological changes. However, it is also obvious that the process must have been active long before the onset of the symptoms, because three weeks after the first sign of pain, well marked calcification was seen in the radiograph.

The aetiology of the condition is obscure. The lack of pyrexia and the normal sedimentation rate make an infective basis unlikely, and there was no history of injury to suggest a traumatic aetiology. Degeneration seems untenable in view of the age of the patient. In fact in one of Silverman's (1954) cases calcification was detected as early as 12 months of age.

Whatever the aetiology, the condition appears to be reversible and in reported cases the calcium deposits have been observed to disappear gradually over a period of months to years. No treatment appears indicated apart from rest and analgesics while there are symptoms.

Summary

A case of calcification of intervertebral discs in a 5-year-old girl is described. Attention is drawn to its infrequency in children, its good prognosis and the reversible nature of the radiological changes.

REFERENCES

Báron, A. (1924). *Jb. Kinderheilk.*, **104**, 357. Quoted by Weens, H. S. (1945). *J. Pediat.*, **26**, 178.
Silverman, F. N. (1954). *Radiology*, **62**, 801.

INTERPOSITION OF THE COLON BETWEEN LIVER AND DIAPHRAGM (CHILAIDITI'S SYNDROME) IN CHILDREN

BY

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In 1910 Chilaiditi published a paper in which he described three adult patients with gaseous abdominal distension and intermittent displacement of the liver by a distended loop of colon. Although there had been some earlier brief reports, for example those of Gontermann (1890), Cohn (1907) and Weinberger (1908), this was the first really detailed account of the condition which has come to be known as Chilaiditi's syndrome.

During the last 45 years many more cases have been reported but very few of these have been children. It will be of some interest, therefore, to record the clinical and radiological findings in four further cases of Chilaiditi's syndrome in childhood and to discuss the aetiology of the condition as suggested by the study of these children.

Case Reports

Case 1. Andrew F. was born in August, 1949. He was first seen in December, 1950, at the age of 16 months. Abdominal distension had been noticed for about a year and more recently there had been some abdominal pain and vomiting. The past history was otherwise uneventful and the parents and a sibling were healthy.

On examination the abdomen was considerably distended and tympanitic. With the child lying supine the liver edge could be felt below the right costal margin. In the erect and left lateral positions, however, there was resonance to percussion over the right hypochondrium continuous with the resonance over the lung, and the edge of the liver could be palpated with some difficulty on the left side of the abdomen. The urine was normal and there were no other important findings.

RADIOLOGICAL EXAMINATION. Radiological investigations were carried out on several occasions over a period of several months. There was invariably gaseous distension of the stomach and intestines. Films taken in the erect position showed the liver to be displaced downwards and to the left, its place being taken by a distended loop of colon (Fig. 1). In the supine position the liver and colon usually occupied their normal positions. On one occasion during the fluoroscopy the ascent of the colon and the displacement of the liver were actually observed as the patient was rotated from the supine to the left lateral position. Fluoroscopy after an opaque meal excluded any form of intestinal obstruction and the interposed loop of bowel was identified as the hepatic flexure.

PROGRESS. During the six months following his first visit to hospital the child had recurrent attacks of severe abdominal pain with vomiting and his mother became aware of his swallowing air. He was admitted to hospital in June, 1951, and put to bed. The attacks promptly ceased, although the abdominal distension persisted and the position of the liver could still be altered with posture.

The patient's progress over the next few years was satisfactory and when last seen in April, 1956, he was having only occasional, mild abdominal pain in the evening and this was rapidly relieved by sitting or lying

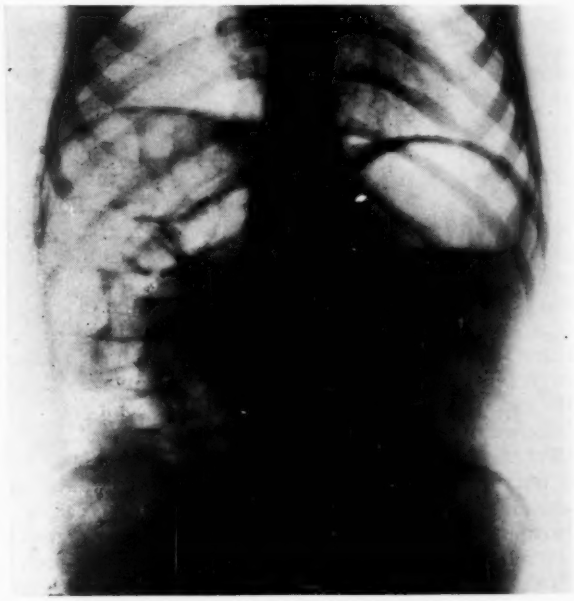

FIG. 1.—Radiograph of the abdomen (erect) in Case 1.

down. His mental and physical development was normal. However, apart from considerable diminution of the abdominal distension, the clinical and radiological findings were unchanged.

Case 2. Ann S. was born in November, 1951. She was admitted to hospital in November, 1954, at the age of 3 years with a history of abdominal distension for most of her life and recent abdominal pain. The mother had also noticed that the child gulped her food and frequently passed flatus, especially if any pressure was applied to the abdomen. The bowels were constipated but there was no history of vomiting. Details of the family and past history were not relevant.

On examination the abdomen was extremely distended. A few dilated veins were seen on the upper abdominal wall and there was visible intestinal peristalsis. The liver was displaced downwards and to the left in the erect position, its lower edge being palpable in the left hypochondrium. Occasionally with the patient lying down the liver could be felt in the normal position. On percussion the whole abdomen was tympanitic and there was no liver dullness. During her stay in hospital the child occasionally complained of slight abdominal pain in the evening. Relief of the constipation did not affect the abdominal distension which was found to be much less marked in the early morning and to increase gradually during the day irrespective of whether the child was kept in bed or allowed up. The displacement of the liver, however, was only demonstrated in the erect position.

RADIOLOGICAL EXAMINATION. In view of the experience with Case 1 radiological investigations were more extensive in this case. Comparison of films taken soon after the child awoke in the early morning with those taken in the late afternoon showed a striking difference in the degree of the abdominal distension. In the morning there was very little gas in the stomach and only slight distension of the colon confined to the descending part, whereas later in the day there was gross distension of the stomach and most of the intestinal tract. These findings confirmed the clinical observation of increasing distension during the day. There were also differences in the position of the liver depending on the time of day at which the films were taken. In the early morning the liver shadow was seen in its normal position below the right diaphragm in both supine and erect films. In the afternoon with the patient erect the liver was displaced downwards, forwards and medially, its exact position being difficult to make out, and a loop of the distended colon occupied the sub-diaphragmatic space (Figs. 2 and 3); in the supine position the liver returned to its normal place on some occasions but not on others. Air swallowing was observed during screening of the abdomen.

PROGRESS. This patient has now been followed for 18 months. For the first year or so she continued to have marked abdominal distension, and occasional abdominal pain during the later part of the day which was relieved by lying down. Recently the symptoms have almost completely subsided but at the latest examination in April, 1956, although the abdominal distension was considerably less, the clinical and radiological signs of interposition with the liver displacement were unaltered.

Case 3. Naomi P. was born in December, 1950, and was 5 years old when first admitted to hospital. Her complaint was of attacks of abdominal pain which had begun some five weeks previously. The pain was quite severe, lasted about half an hour and was relieved by belching and passing flatus; it occurred most commonly in the late afternoon. She never vomited but was sometimes constipated and her appetite, previously good, had become poor. Her abdomen had been unduly distended for as long as the parents could remember. There were no siblings and the family and past history were not relevant to the present condition.

The clinical findings were similar to those in the previous cases. The increasing daytime distension of the abdomen was particularly well marked, the circumference of the abdomen increasing from 18 in. at 5 a.m. to 24 in. at 2 p.m. In the erect position and occasionally in the afternoon in the supine position the liver dullness was absent and the liver itself was not palpable. The child's physical and mental development was normal. There were no abnormal physical signs and laboratory examination of the urine and faeces showed no abnormality.

RADIOLOGICAL EXAMINATION. The typical features of the syndrome were again demonstrated. There was progressive daytime distension of the whole alimentary tract. Supine films (Fig. 4) showed the normal anatomical relations of liver and colon but in the erect position the colon was interposed between liver and diaphragm with displacement of the liver (Fig. 5). On one occasion the interposition was only partial, the liver being displaced forwards but not downwards. An opaque meal passed down the alimentary tract without obstruction and air swallowing was observed during the examination.

PROGRESS. This child's progress has so far been followed for only three months. During this time some attempt has been made to lessen the abdominal distension without much success. Oral administration of charcoal biscuits and a carminative mixture produced no obvious improvement, and the wearing of an elastic abdominal belt has, if anything, increased the child's discomfort. She still vomits occasionally and is troubled by the progressive daytime distension but is otherwise quite well and has gained weight.

Case 4. Elizabeth F. was born in September, 1951, and was 4½ years old when admitted to hospital in February, 1956. Following an attack of gastro-enteritis two months before admission she had complained of anorexia, recurrent abdominal pain and vomiting, frequent passage of flatus and abdominal distension, which was most marked at the end of the day. For some time past she had been noticed to swallow air. The parents and a sibling were healthy and there were no incidents of note in the past history.

On examination the physical signs of liver displacement were present in the erect position and the typical progressive abdominal distension was observed. The

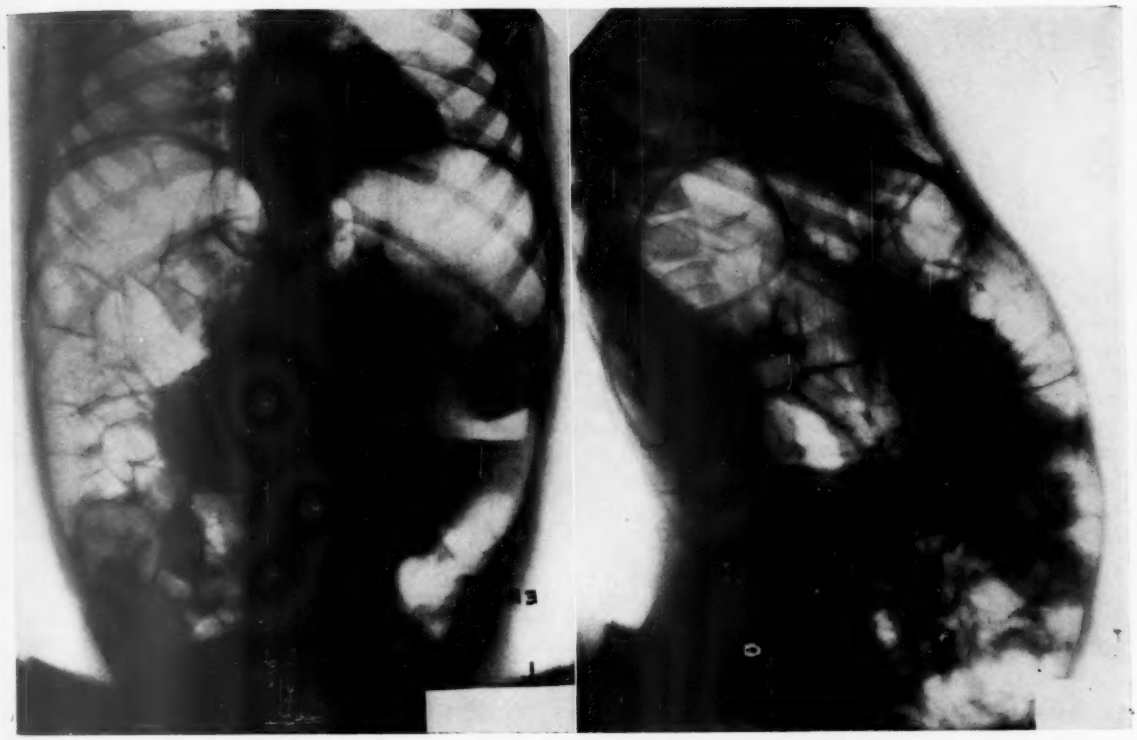

FIG. 2. FIG. 3.

FIGS. 2 and 3.—Antero-posterior and lateral radiographs of the abdomen (erect) in Case 2. These films were taken in the late afternoon and illustrate the extreme degree of gaseous distension of the stomach and intestines.

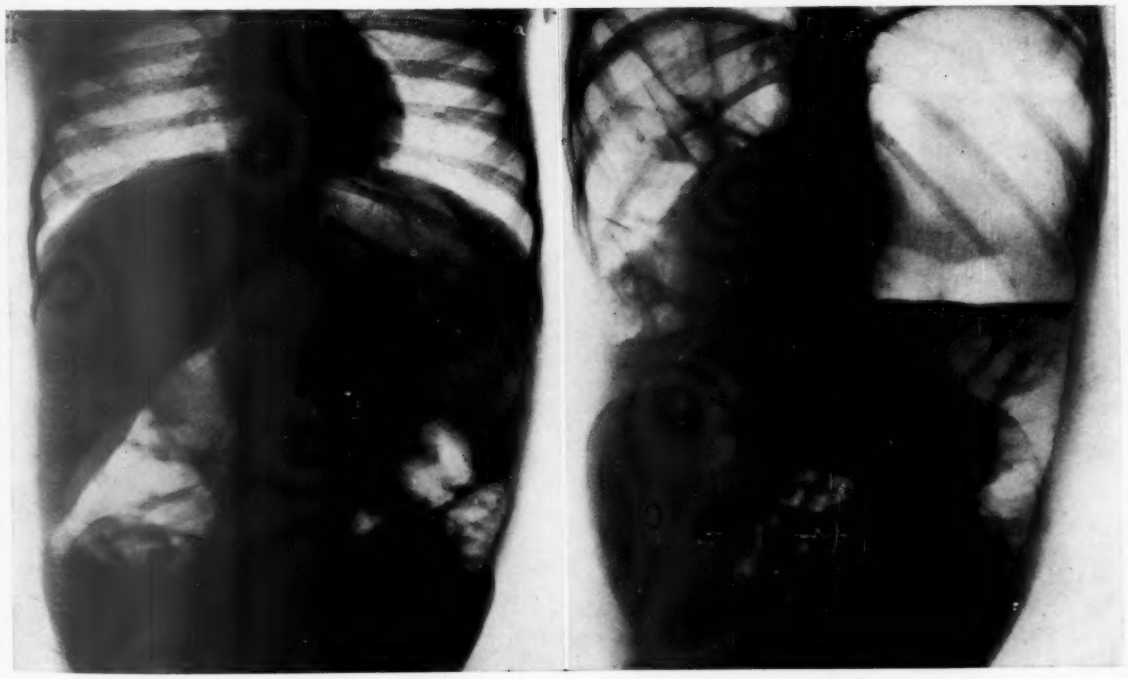

FIG. 4. FIG. 5.

FIGS. 4 and 5.—Radiographs of the abdomen (supine and erect) in Case 3. In the supine position (Fig. 4) the liver and colon occupy their normal positions. In the erect position (Fig. 5) there is interposition of the colon and displacement of the liver. The huge gas bubble in the stomach is typical of aerophagy.

urine was normal and there were no other abnormalities on clinical examination.

RADIOLOGICAL EXAMINATION. The familiar radiological features were present (Fig. 6). Gaseous distension of the alimentary tract was far greater in the later part of the day. Air swallowing was observed on screening and there was no evidence of intestinal obstruction. Interposition of the colon and varying degrees of displacement of the liver was seen in films taken with the patient erect; the normal anatomy was restored in the supine position.

PROGRESS. This patient has been under observation for about four months. During this time she has made a complete recovery. She wore an abdominal belt for three months after her discharge from hospital but had left it off for one month before the last examination when she was found to have no clinical or radiological abnormality.

Discussion

These cases illustrate a well-defined clinical syndrome, the main features of which are marked diurnal abdominal distension and interposition of the colon between the liver and the diaphragm in the erect position. The commonest symptom is abdominal pain which is sometimes quite severe and associated with vomiting. This pain occurs typically towards the end of the day when the abdominal distension is maximal and is less frequent and much less severe when the patient is in bed. Other, less common symptoms are anorexia, constipation and the frequent passage of flatus. The distinctive physical signs are those of abdominal distension with absent liver dullness, and the liver edge may be palpable somewhere on the left side of the abdomen. There are no other abnormalities or signs of retardation of physical or mental development.

The diagnosis may be confirmed by radiology if, in the erect position, the striking appearance of a distended loop of colon under the right dome of the diaphragm is present and the liver is to a greater or lesser degree displaced. In addition, haustral markings establish the fact that the subphrenic gas is within the colon and not free in the peritoneal cavity. The generalized nature of the distension, which extends right down to the lower rectum, and the absence of large faecal masses help to distinguish the radiological picture from that of Hirschsprung's disease and chronic constipation of the 'terminal reservoir' type. It is important to ensure that radiographs are taken in the erect position and that a lateral view is included, since interposition does not usually occur when the patient is supine and the position of the liver may be in doubt on an antero-posterior film.

The literature on interposition of the colon in adults is extensive and several authors have each collected over 20 cases (Uspensky, 1928; Trémolières and Tardieu, 1931; Kolju, 1938; Hubacher, 1946; Torgersen, 1951). The incidence of the condition in adults appears to be about 1 per 1,000 radiological examinations made in the erect position, i.e., chest films or screening (Uspensky, 1928; Kolju, 1938). This figure might, however, be considerably less if lateral radiographs had more often been taken to confirm the displacement of the liver. A distended colon lying anterior to the liver, and therefore not truly interposed, may in an antero-posterior film obscure the liver shadow, giving the false impression that the liver is displaced. The scarcity of published reports concerning children suggests that the condition is rare in this age group but cases may have been missed because radiographs of children with abdominal distension are not normally taken in the erect position. The fact that the present series of four cases* was collected over the space of only a few years suggests that such cases are not exceptionally uncommon in children. In adults both sexes are affected, males more frequently than females, and there is a suggestion of a geographical distribution in the fact that cases have been reported most frequently by authors on the continent of Europe. A recent extensive review of the subject (Baum and Karpati, 1954) lists 57 references of which only four are in the English language.

Baum and Karpati (1954) discuss the aetiology of Chilaiditi's syndrome in some detail. They point out that the liver is held in position mainly by a sort of sub-diaphragmatic suction and suggest that certain abnormalities can disturb this relationship between liver and diaphragm, allowing the liver to descend under the influence of gravity and the colon to take its place. Such abnormalities, which may act singly or in combination, include intestinal distension, diaphragmatic paralysis, abnormalities of the size or suspension of the liver, traction on the liver by adhesions in the region of the duodenum, and ascites. The evidence that some of these factors, e.g., abnormal suspension of the liver and the traction effect of the peri-duodenal adhesions, play any part is, however, unconvincing.

There may be different degrees of interposition and liver displacement. In the complete form, illustrated by the present cases, the colon lies above the liver, contact between liver and diaphragm is broken and the liver is displaced downwards, forwards and medially. Interposition is incomplete or partial when the colon does not get above the liver but lies laterally (Fig. 7) or posteriorly (Figs. 8 and 9). The liver is then displaced medially or

* In addition to the four cases studied in detail three further cases of complete interposition have come to our notice during the preparation of this paper and one case of partial interposition is briefly described in the legend to Fig. 7.

FIG. 6.

FIG. 7.

FIG. 6.—Radiograph of the abdomen (erect) in Case 4.

FIG. 7.—Part of a radiograph of the abdomen (erect) of a girl aged 8 years showing a partial (lateral) interposition of the colon with medial displacement of the liver. This was a chance finding; the patient had pneumonia and there were no abdominal symptoms. The interposition has not been seen again despite repeated radiological examinations.

FIGS. 8 and 9.—Antero-posterior and lateral radiographs of the abdomen (erect) in Case 3. On this occasion the interposition was incomplete (posterior). The colon has risen behind but not above the liver which is displaced forwards.

FIG. 8.

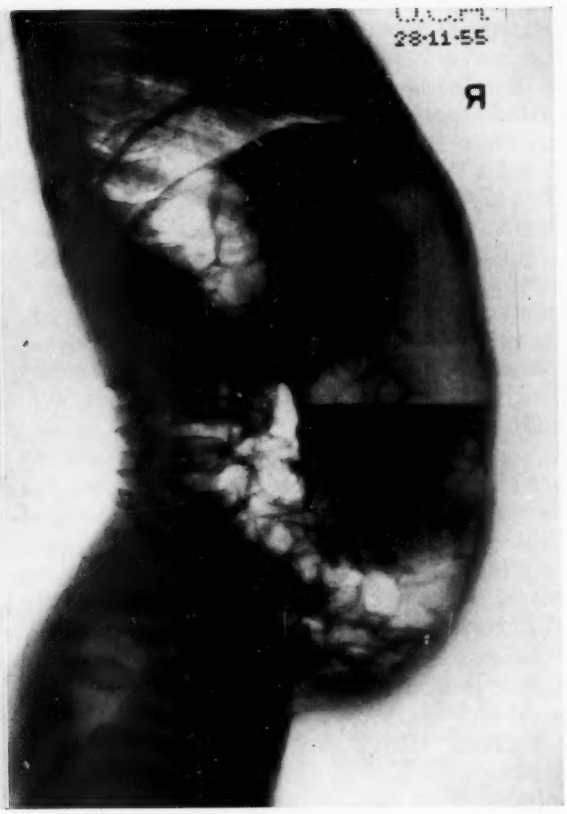

FIG. 9.

forwards but not downwards. Chilaiditi's (1910) original cases were of this type. Presumably such factors as the intra-abdominal pressure, the degree of distension of the stomach and intestines and the mobility of the colon determine whether the interposition shall be partial or complete. Occasionally the interposition is transient, being detected for only brief periods without further recurrence. In such cases there is usually a very temporary cause for the distension of the gut such as an acute respiratory infection (Grüber, 1937; see also Fig. 7) or pregnancy (Hunter and Rapp, 1953). In most cases, however, including the four children under discussion, the interposition persists, although only in the erect position, over a much longer period and occasionally the colon becomes permanently fixed in its abnormal position by adhesions between it and the liver or diaphragm (Rogers, 1935; Choussat and Choussat-Clausse, 1937). Very rarely other parts of the intestinal tract, such as the ileum (Baum and Grasser, 1952), may become interposed.

Abdominal symptoms such as pain, vomiting, flatulence and constipation, were present in about half the reported adult cases and in addition to the development of adhesions a further important complication may arise, namely torsion of the interposed loop of bowel which gives rise to the signs and symptoms of acute intestinal obstruction. This may lead to an unnecessary laparotomy either because in the radiograph the presence of a gas-filled loop of colon under the diaphragm is misinterpreted as free gas in the peritoneal cavity (Pendergrass and Kirk, 1929) or because the importance of posture in the relief of interposition is not realized. Hunter and Rapp (1953) reported a case of temporary interposition with torsion of the interposed hepatic flexure demonstrated by barium enema. The symptoms of obstruction were rapidly relieved when the colon was released and the normal anatomy restored by alteration of the patient's posture during radiological examination.

As far as children are concerned very little has been added in recent years to the clinical description by Gontermann (1890) of an infant with abdominal distension and the physical signs of liver displacement (*Wanderleber*). Grüber (1937) and Arce (1946) also described cases and in addition gave brief accounts of the radiological findings.

Such is the historical background of Chilaiditi's syndrome in adults and children against which the observations on the present cases were analysed. The primary abnormality in these children is abdominal distension almost certainly due to the aerophagy which was observed in all four cases either by the parents or by the radiologist. The progressive distension of the alimentary tract during the day with tremendous dilatation of the stomach, the diminution of the distension by night and the absence of intestinal obstruction are further facts in support of a diagnosis of aerophagy. The reason why these children should acquire the air swallowing habit to such a marked degree is not obvious. None of them appeared to have any significant emotional disturbance to suggest a psychological cause. Since the abdominal distension persists even when the patient is kept in bed it is apparently independent of colonic interposition and liver displacement which only take place in the erect position. Kolju (1938) studied the mechanism of interposition in adults by fluoroscopy. With the patient upright the colon was distended with air through a rectal tube and was seen to rise up and insert itself between the liver and the diaphragm. At this point displacement of the liver took place. It is probable that this is exactly the sequence of events in the present cases with air swallowing as the cause of the distension. There is no reason to suggest any abnormality of the liver or its suspensory ligaments since the normal liver is sufficiently mobile to allow considerable displacement to take place as, for example, in cases of pneumoperitoneum either artificially induced (Fig. 10) or spontaneous (O'Donoghue, 1956).

FIG. 10.—Radiograph of the chest and abdomen of a boy aged 12 in whom an artificial pneumoperitoneum has been induced for pulmonary tuberculosis. There is considerable infero-medial displacement of the liver.

One further fact requires explanation. In a search for further examples of this syndrome radiographs, taken in the erect position, of other children with abdominal distension were examined. These included 10 cases of Hirschsprung's disease and four cases of aerophagy, in all of which the distension of the colon was comparable with that of the cases of Chilaiditi's syndrome. Nevertheless, in no instance was there any evidence of interposition or liver displacement. In addition, therefore, to colonic distension and the effect of gravity some further factor is necessary if interposition is to take place. It seems probable that this factor is an unusual mobility of the ascending colon and hepatic flexure due to the presence of an ascending mesocolon. There is evidence from operation reports (Rogers, 1935; Herget, 1951) and necropsy reports (Pendergrass and Kirk, 1929; Soupault, 1930) that this mobility of the colon exists in adult cases. In children a highly-placed caecum and an apparent redundancy of the hepatic flexure are normal anatomical variants (Bryant, 1924; Caffey, 1956) so that abdominal distension might by chance occur in a child with a mobile ascending colon.

It is concluded, therefore, that in the present group of children the aetiology of interposition of the colon is primarily abdominal distension of a severe degree resulting from aerophagy. Unusual mobility of the ascending colon combined with the effect of gravity result in ascent of the distended bowel into the sub-diaphragmatic space with consequent infero-medial displacement of the liver. These abnormalities associated with the symptoms and distinctive radiological picture already described constitute a particular form in children of the syndrome which is probably best termed 'interposition of the colon between liver and diaphragm' or more simply 'interposition of the colon'. This title is preferable on the grounds of euphony to 'hepatodiaphragmatic interposition of the colon' which has been used by some authors. The eponymous title 'Chilaiditi's syndrome' is not strictly correct since the cases described by Chilaiditi (1910) were adults with a partial form of interposition and not entirely comparable with those under discussion.

The pain and vomiting in these children could be entirely explained by the degree of intestinal distension and it might be argued that the abnormal position of the liver and colon play no part in their production. However, children with quite marked abdominal distension due to aerophagy without interposition seldom complain of severe pain, whereas in three of the present cases (Cases 1, 3 and 4) the symptoms were at times bad enough to suggest the possibility of intestinal obstruction. In Case 1, before the nature of the diagnosis has been appreciated, laparotomy was seriously considered and was only avoided by the timely disappearance of the symptoms after the patient had been put to bed. The frequent observation of this relief of acute abdominal symptoms by a change of posture from upright to supine indicates that, at least on some occasions, the symptoms are due to colonic or liver displacement rather than to distension. Since experience in patients with artificial pneumoperitoneum suggests that liver displacement *per se* does not cause abdominal pain it is probably the interposition of the colon which is to blame. A possible explanation is that the symptoms are due, as in certain adult cases previously mentioned, to obstruction brought about by torsion or incarceration of the interposed loop of colon as it becomes more and more distended in the relatively confined space above the liver. Releasing the interposition by placing the patient supine would relieve this obstruction and hence the symptoms. The amount of distension varies from case to case and from time to time in any one case and it is possible to imagine a degree of distension of the colon sufficient to give rise to interposition but not severe enough to cause obstruction. Hence the fact that in Cases 1 and 2 there has been a reduction in distension and in the severity and frequency of symptoms, although in both cases interposition of the colon persists. This theory would also account for the absence of symptoms in many adult cases and for such cases as the child whose radiograph is illustrated in Fig. 7, in which the distension is minimal and the resulting interposition incomplete and symptomless.

In view of the relatively short period of observation and the small number of children studied it is not possible to be certain of the natural history of the syndrome in these children. The anatomical abnormality has so far persisted for five and a half years in Case 1 and for 18 months in Case 2, although in both cases the air swallowing and consequently the distension and pain are steadily diminishing. If this improvement is maintained and the colon becomes less mobile a spontaneous cure, such as appears to have occurred in Case 4, might be expected. If, however, the mobility of the colon is permanent the persistence or recurrence of interposition would always be possible depending on the presence of abdominal distension, whether it were due to aerophagy or to any other cause. Since the condition is comparatively common in adults it is possible that some childhood cases do, in fact, persist into adult life.

Treatment for the condition has been attempted

in only two of the children (Cases 3 and 4). In the light of the spontaneous improvement in Cases 1 and 2 the necessity for any treatment is doubtful and the assessment of its value difficult. Prevention of the aerophagy is obviously desirable but in children of this age difficult to achieve. Carminatives had no effect on the intestinal distension in Case 3. The effect of wearing an abdominal belt was tried in Cases 3 and 4, and, although in Case 4 this measure was accompanied by an apparent recovery, it is difficult to believe that this was anything but coincidental. On balance there does not so far appear to be any significant difference in progress between the treated and untreated cases. Operative fixation of the colon (Rogers, 1935) or liver (Schenck, 1938) has been suggested to prevent interposition taking place and to avoid complications. Until the possibility of permanent spontaneous cure is excluded such drastic therapy does not seem to be justified. Surgical measures to divide established adhesions between the colon and the diaphragm would perhaps be more reasonable but it is difficult to see how this complication would be diagnosed on clinical grounds.

In conclusion it is suggested that the syndrome of interposition of the colon in children is a definite entity, easily recognized by a typical clinical and radiological picture, and is of some importance by reason of the symptoms it may produce and the possible complication of intestinal obstruction which may lead to an unnecessary laparotomy if the nature of the condition is unrecognized. It is very probable that more cases would be discovered if the existence of the syndrome were more widely appreciated.

Summary

The syndrome of interposition of the colon between liver and diaphragm is described.

A clinical and radiological study of four cases of this syndrome in childhood is reported. It is concluded that in these cases the primary abnormality is abdominal distension due to aerophagy and that unusual mobility of the distended colon permits its ascent into the sub-diaphragmatic space in the erect position, with consequent displacement of the liver.

The syndrome is probably not uncommon in children despite the rarity of published reports.

We are indebted to the following paediatricians who have allowed us to study and record their cases and have given much helpful advice in the preparation of this paper: Dr. Helen Mackay (Case 1), Dr. Richard Dobbs (Case 2), Dr. Bernard Schlesinger (Case 3), Dr. George Ormiston and Dr. Wilfrid Sheldon (Case 4). We should also like to thank Drs. W. F. Richards and B. C. H. Ward of High Wood Hospital for Children for their advice concerning artificial pneumoperitoneum and for the radiograph reproduced in Fig. 10. Dr. L. G. Blair kindly provided several of the other radiographs.

References

Arce, G. (1946). *Acta pediatr. esp.*, **4**, 747.
Baum, G. and Grasser, H. (1952). *Fortschr. Röntgenstr.*, 77, 616.
—— and Karpati, A. (1954). *Med. Mschr.*, **8**, 221.
Bryant, J. (1924). *Amer. J. med. Sci.*, **167**, 499.
Caffey, J. (1956). *Pediatric X-ray Diagnosis*, 3rd ed., p. 546. Chicago.
Chilaiditi, D. (1910). *Fortschr. Röntgenstr.*, **16**, 173.
Choussat and Choussat-Clausse (1937). *Bull. Soc. Radiol. méd. Fr.*, **25**, 147.
Cohn, M. (1907). *Verh. dtsch. RöntgGes.*, **3**, 66.
Gontermann (1890). *Dtsch. med. Wschr.*, **16**, 1043.
Grüber, E. (1937). *Ibid.*, **63**, 1113.
Herget, R. (1951). *Beitr. klin. Chir.*, **183**, 83.
Hubacher, O. (1946). *Schweiz. med. Wschr.*, **76**, 554.
Hunter, H. L. and Rapp, R. (1953). *Radiology*, **61**, 67.
Kolju, K. J. (1938). *Amer. J. Roentgenol.*, **39**, 928.
O'Donoghue, P. D. (1956). *Lancet*, **1**, 189.
Pendergrass, E. P. and Kirk, E. (1929). *Amer. J. Roentgenol.*, **22**, 238.
Rogers, J. C. T. (1935). *Illinois med. J.*, **68**, 264.
Schenck, S. G. (1938). *Arch. Surg. (Chicago)*, **36**, 766.
Soupault, R. (1930). *Arch. Mal. Appar. dig.*, **20**, 350.
Torgersen, J. (1951). *Amer. J. Roentgenol.*, **66**, 747.
Trémolières, F. and Tardieu, A. (1931). *Arch. Mal. Appar. dig.*, **21**, 1154.
Uspensky, A. (1928). *Fortschr. Röntgenstr.*, **37**, 540.
Weinberger, M. (1908). *Med. Klin.*, **4**, 584.

BENIGN HAMARTOMA OF THE LIVER

BY

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Sheehan (1930) when describing a malignant liver tumour in a young child, first brought together a number of such tumours previously described under a variety of names, such as 'sarcoma', 'endothelioma' or 'angeiosarcoma', and pointed out that they were probably all derived from rests of undifferentiated mesenchymal cells and were in fact embryonic growths. The tumour he described consisted largely of undifferentiated mesenchyme forming cysts lined with bile-duct epithelium, but in one cyst the basic cells showed malignant features with vascular invasion. In other places they had differentiated into myxoma, fibrous tissue, acinar tissue and striated muscle.

These tumours are evidently rare and few later reports are available (e.g., Nissel, 1928; Roth, 1938; Webster, 1938; Wells, 1940; McRae, 1935). All appear to accept an embryonic origin for the tumours and, indeed, Roth termed his a 'unilayered teratoma'. All the tumours so far reported appear to have been malignant with multiple vascular metastases within the liver but a curious absence of metastases to other sites.

Case Record

A girl aged 18 months was brought to hospital by her mother who had noticed swelling of the child's abdomen for about six months. The child appeared perfectly fit apart from the obvious swelling, which was due to a firm, smooth, solid tumour filling most of the abdomen and whose origin could not be determined clinically. There appeared to be nothing relevant in the family history and the child was the result of a normal pregnancy and delivery.

At laparotomy an enormous, smooth tumour was found suspended from the under surface of the liver by a narrow pedicle and was removed without undue difficulty. The remaining abdominal viscera appeared superficially normal. The child made an uninterrupted recovery.

The gross tumour was ovoid, about 30 cm. × 30 cm. × 20 cm., with a smooth surface covered by peritoneum and with no obvious adhesions. The cut surface showed many small cysts of up to 1 cm. across and containing colourless, gelatinous material. The intervening substance appeared homogeneous and of a deep red colour and was quite firm.

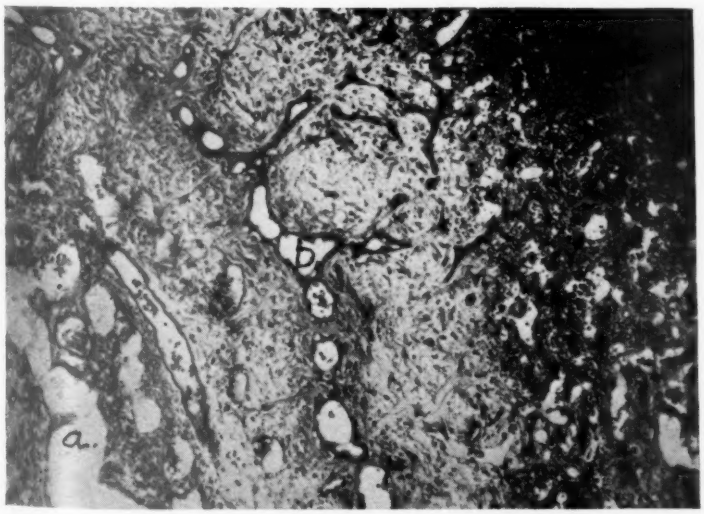

FIG. 1.—Section of tumour from near its pedicle showing vascular channels on the left (a), tubes of bile duct epithelium in the middle (b) and well-formed liver parenchyma to the right, the whole filled in by loose mesenchymal tissue (×88).

Histology. A number of blocks were taken from different areas, but all showed a very similar, fundamentally an identical, picture, except that there was more normal liver tissue in the blocks taken from near the pedicle than was found elsewhere. There were then islands of normal, perfectly-differentiated liver tissue. Most of the tumour, however, consisted of ramifying bile ducts, or rather, since they had no muscular coats, tubes of bile duct epithelium. They were of all sizes and the cysts appeared to be dilatations of them. No malignant features were found in the epithelium in the numerous blocks taken. The second type of tissue consisted of numerous, thin-walled vascular channels, which, however, were well developed and showed no malignant features, although in places they were so

closely crowded as to resemble a cavernous haemangioma. No other type of blood-vessel-forming tissue was seen and it was evident that the tumour was not fundamentally any type of true angioma. The third, and most obvious, element in the tumour was loose-textured connective tissue. Once more, this was perfectly well differentiated and no malignant features were seen. However, this tissue was very great in amount and evidently constituted an essential part of the tumour and could not be regarded as a mere supporting framework. All these features are shown in Fig. 1.

Discussion

In the tumour described, all the tissue elements were perfectly differentiated in all areas examined, no stages in this differentiation were seen, and all the elements were such as can be found in the mature liver. It becomes, therefore, a matter of definition whether or not it fits Sheehan's conception of the origin of similar tumours from undifferentiated mesenchymal cells. Most of the other tumours described have contained other tissues which are not normally present in the developed liver, e.g., Sheehan's tumour which contained striped muscle. However, all these other tumours showed malignant features, i.e., their cells, or at least some of them, had not differentiated fully. It would appear, then, that the present one must either be regarded as taking its origin from mesenchymal cells better differentiated than those which caused the other tumours or as arising from four different tissues after they had become differentiated. The former theory places less strain on the imagination.

The present writer has always been sceptical of the existence of hypothetical 'undifferentiated' cells whose existence can only be inferred by what is supposed to have developed from them, at any rate when dealing with adult tissues outside the gonads. The mass found in this child's liver contains adult-type tissues, fully-differentiated, but in abnormal proportions. It would seem best, therefore, to describe it as a 'hamartoma', a term which implies no theory of its origin.

Summary

Another of the very rare embryonic tumours of the liver is reported. It contained well differentiated tissues and was benign. Most of those described previously have been malignant in some part. The present example is probably best classified as an hamartoma.

References

McRae, F. W. (1935). *Amer. J. Surg.*, **28**, 575.
Nissel, W. (1928). *Virchows Arch. path. Anat.*, **269**, 446.
Roth, F. (1938). *Frankfurt. Z. Path.*, **52**, 163.
Sheehan, H. L. (1930). *J. Path. Bact.*, **33**, 251.
Webster, R. (1938). *Med. J. Aust.*, **2**, 381.
Wells, H. G. (1940). *Arch. Path.* (*Chicago*), **30**, 535.

HYDROCEPHALUS AFTER INTRA-UTERINE FUNGAL INFECTION

BY

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(RECEIVED FOR PUBLICATION OCTOBER 30, 1956)

Fungal infections of the nervous system are uncommon but are mentioned by Russell (1949) as a possible cause of hydrocephalus. Intra-uterine meningitis from any cause has been reported only once. Crosby, Mosberg and Smith (1951), in reporting this case, reviewed the literature on meningitis of the newborn up to 1951 and could find no other case acceptable as having an inception in the intra-uterine period.

The following case appears to be unique in that hydrocephalus resulted from an intra-uterine attack of meningitis due to a fungus.

FIG. 2.—Lining of lateral ventricle showing roughening and granules.

Case Report

Baby S. was born on August 8, 1954, after a short, forceful labour lasting two hours. The presentation was vertex, L.O.A. The mother's health had been normal throughout the pregnancy. There was no history suggestive of vaginal thrush on close questioning, and antibiotics had not been given during the pregnancy. The only previous child, born in 1949, was alive and well.

Conception in the present case had followed closely on dilatation and curettage and tubal insufflation, carried out because of apparent infertility.

The baby, a boy, weighed 7½ lb. at birth. He was slow to breathe and cry but responded well to oxygen and incubation. At the time of delivery some haemorrhagic areas were noted on the face, attributed to bruising at delivery. These faded within a fortnight. Soon after birth it was noticed that the baby's sucking and swallowing reflexes were poor and for the first fortnight he was tube fed. For the first 10 days his tenure of life was precarious. Twitching of the left eyelid was first noted on the third day and subsequently both eyes and the left side of the face twitched at intervals. Examination on the fifth day showed undue separation of the skull sutures and a diagnosis of hydrocephalus was suggested.

From the end of the second week there was some improvement in the baby's condition. Sucking improved and bottle feeding was started. The head diminished in size from a circumference of 15½ in. on the 18th day to 14½ in. on the 29th day. On the 33rd day he had a convulsion and began to pass frequent green motions. His condition progressively deteriorated and he died on the 37th day.

Post-mortem examination was performed by the author 18 hours after death. The body was that of a normally developed but

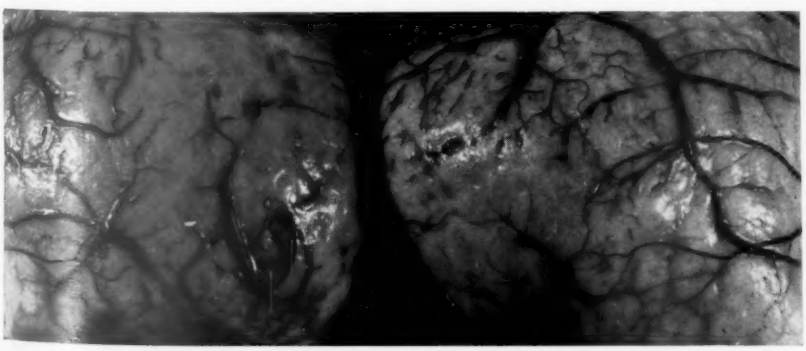

FIG. 1.—Occipital poles showing organized exudate in subarachnoid space.

FIG. 3.

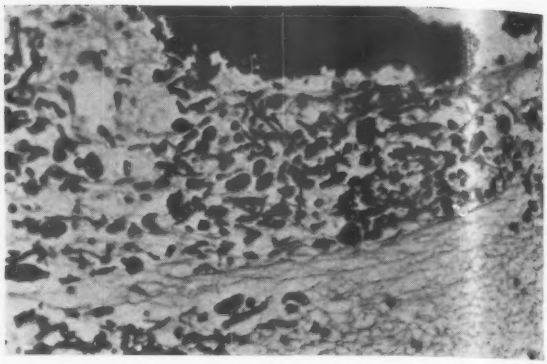

FIG. 5.

FIG. 3.—Low-power view of a section of the area shown in Fig. 1. Haematoxylin and eosin.

FIG. 4.—Section of lining (low-power view) of lateral ventricle. Note layer of organized exudate and dark, partly calcified fungal material Haematoxylin and eosin.

FIG. 5.—P.A.S.-stained section (high-power view) of area seen in Fig. 4, showing fungal spores and mycelia. The darkly staining mass at the top is a calcifying mass of spores.

FIG. 4.

rather poorly nourished male infant weighing 3,280 g. The trachea and bronchi contained yellowish mucoid material and the lungs showed basal collapse and congestion. The small intestine was slightly dilated and contained watery yellowish fluid and the contents of the large bowel were also watery and yellow.

The skull measured 14 in. in circumference, the cranial bones were thinned and the sutures were widened. The cerebral hemispheres were tense and distended with marked flattening of the sulci. A striking feature was the obliteration of sulcal markings over the occipital poles by pale organized exudate (Fig. 1). There were a few fine adhesions about the base of the brain. There was gross hydrocephalus involving the lateral and third ventricles. The corpus callosum was grossly thinned. The aqueduct was narrow but patent. The lining of the lateral ventricles was roughened at some points and there were scattered small yellowish projections into the lumen (Fig. 2).

The possibility of toxoplasmosis was entertained and the eyes were examined and sectioned but were normal macroscopically and microscopically.

Sections of the exudate over the occipital pole and to a lesser extent at other points, mainly at the base of the brain, showed marked meningeal thickening with adhesions to the pia (Fig. 3).

No organisms could be demonstrated in the organized exudate which showed very sparse lymphocytic infiltration. Sections from the lining of the lateral ventricles showed partial loss of the ependymal layer, the cells of which were elsewhere largely flattened to cuboidal. Beneath a layer of glial scarring, and at some points penetrating more deeply into the brain substance, were irregular masses of partly calcified necrotic material and structures identifiable by P.A.S. stains as hyphae and spores of a fungus (Figs. 4, 5). These masses of fungi and necrotic material formed the yellowish granules visible macroscopically. There was a sparse lymphocytic infiltration around the fungal masses.

Sections from a number of other organs, including lung, liver and pancreas, showed no evidence of disseminated fungal infection.

The final morbid anatomical diagnosis was hydrocephalus after intra-uterine fungal infection, gastroenteritis and inhalation of vomitus.

Comment

Was the infection truly intra-uterine? There are several reasons for this belief. First the distribution of exudate over the occipital pole is best explained by the baby presenting as a vertex in the L.O.A. position when the occipital poles would be dependent. Secondly the histological appearances with well established scarring and calcification suggest a longer duration of the inflammatory process than five weeks. Thirdly the baby was feeble from birth and hydrocephalus was suspected from as early as the fifth day. It is hardly likely that hydrocephalus could develop in such a short time if a post-natal infection were postulated.

Source of Infection. Monilial vaginal infections are common during pregnancy and it is possible that this patient had a subclinical infection which in some way reached the placenta and was transmitted through it. Another possibility is that the infection was introduced to tubes or uterine cavity in the course of the dilatation and curettage and tubal insufflation carried out not long before conception took place. The infecting organism passing through the placenta may have reached the choroidal plexus and primarily infected the lateral ventricles. The small calibre of the aqueduct could have diminished the spread of infection to the meninges, or the absence of demonstrable organisms in the meninges might be due to the more efficient response of the meninges to infection.

Nature of the Infection. Unfortunately no cultures were made before fixation of the brain so that identification of the infecting organism is incomplete. The presence of septate pseudomycelia and small spores suggests that *Candida albicans*, the most likely pathogen, is responsible for this infection.

Cause of the Hydrocephalus. The clinical course with apparent diminution in the degree of hydrocephalus suggests that a blockage in the aqueduct may have resolved. Morris, Kalz and Lotspeich (1945), describing a case of monilial meningitis, similarly noted that the reactive process was greater in the ventricular cavities than in the subarachnoid space.

Summary

A case is described of hydrocephalus in an infant, due to a fungal infection of the meninges. Reasons are given for the belief that the infection was intra-uterine.

I have to thank Dr. L. C. Averill for permission to publish this case and Drs. D. T. Stewart and G. C. T. Burns and Professor J. A. R. Miles for their help and advice.

References

Crosby, R. M. N., Mosberg, W. H. and Smith, G. W. (1951). *J. Pediat.*, **39**, 94.

Morris, A. A., Kalz, G. G. and Lotspeich, E. S. (1945). *Arch. Neurol. Psychiat. (Chicago)*, **54**, 361.

Russell, D. S. (1949). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*. No. 265.

BOOK REVIEWS

Radiology of the Alimentary Tract in Infancy. By ROY ASTLEY. (Pp. viii+287; 137 plates. 50s.) London: Edward Arnold.

The value of the radiological examination of the alimentary tract in infancy has been recognized during recent years. The radiological examination of infants requires special techniques which are not described in textbooks of radiology, paediatrics or surgery. The author has tried to make good this deficiency and has achieved his aim in a book which is based largely on his own experience.

The first part on the oesophagus contains sections on atresia, disorders of swallowing, oesophagitis, duplications and various extrinsic and intrinsic abnormalities. This section, the second on the diaphragm, and the third on the stomach and duodenum, give an excellent account of the many abnormalities of these structures which are peculiar to infancy and describe methods which the author has found to be effective. The case records have been skilfully chosen to illustrate and emphasize points made previously in the text.

The remaining sections on the small intestine, colon, rectum, and miscellaneous conditions of the liver, pancreas, and retroperitoneal tissues are also more than adequate, but conditions of extreme rarity might have been in small type instead of some of the case reports illustrating diagnostic difficulties which enhance the value of this section.

Clinicians may doubt the value of radiology in the diagnosis of acute appendicitis while radiologists may feel that clinicians give them too few opportunities to investigate babies who vomit persistently. The author has demonstrated how helpful radiology may be in cases of so-called feeding disorder, but he does not indicate in how many cases the examination is negative or what percentage of patients are examined radiologically.

The book is strongly recommended not only to radiologists who will learn technical methods applicable to small subjects, their dangers and their fallacies, but also to paediatricians and surgeons, many of whom will now expect greater assistance from their radiologists in the elucidation of difficult cases of alimentary tract diseases.

The author is to be congratulated in writing on a somewhat neglected field of radiology, while credit must also go to the publishers for the quality of reproduction of the numerous radiographs. The reviewer found only one error in spelling and that in a proper name, surely unusual accuracy for a new book, or better, for a first edition, which will surely be followed by further editions.

Year Book of Pediatrics, 1956-1957. Edited by SYDNEY S. GELLIS. (Pp. 480; 134 figures. 51s.; $6.75). Chicago: Year Book Publishers; distributed in the U.K. by Interscience Publishers. 1956.

This paediatric annual conforms to the tradition established in the last decade, its only departure therefrom being that perhaps one-third of the articles abstracted are from sources other than the North American literature.

Most of the journals abstracted, apart from the United States and Canada, originate in the NATO countries, and practising paediatricians read these journals or are aware of their contents. There must be much work of interest appearing in non-NATO languages in journals from non-NATO countries, not seen or too difficult to read by the average English-speaking paediatrician. In order to obtain a more global comprehension of advances in children's disease, would it be asking Dr. Gellis too much if in future editions of the Year Book of Pediatrics some attention could be paid to the journals of the non-NATO countries to which the ordinary person does not have access?

The 1956-57 volume abstracts some 350 articles and many of the abstracts are followed by invited criticism or comment. The volume is as beautifully produced as always.

The Medical Annual. Edited by SIR HENRY TIDY and R. MILNES WALKER. (Pp. xi+548; 37 plates. 38s. 6d.) Bristol: John Wright. 1956.

This year book, now in its 74th year, is too well established in the esteem of the profession to require commendation. No volume of the sort can be comprehensive but it covers a vast field, has an excellent index, and the writers have provided material which will interest members of all branches of medicine. The paediatrician will find many articles dealing with subjects in his own field, besides many which he will read for their general interest. The editors draw special attention to an excellent review of recent work on poliomyelitis, including an account of field trials of the vaccine, and also to an article on steatorrhoea. The latter ranges from fat absorption and excretion, aetiology and prognosis in coeliac disease, and radiological appearance of the small intestine in idiopathic steatorrhoea to sprue-like syndromes associated with stagnation in a blind loop of gut, sprue-like syndromes with agammaglobulinaemia, and to 'intestinal lipodystrophy', a syndrome new to the reviewer which exhibits the features of sprue and a migratory polyarthritis.

Advances in cardiac surgery naturally receive attention and the article on coarctation of the aorta indicates increasing recognition of its heavy mortality in infancy and the possibilities of treatment at this age. An article on vital statistics gives a great array of facts; one which

caught the eye of the writer, struck by the increasing proportion of psychological disorders in out-patients at a children's hospital, was the information that of men discharged from the army for medical reasons, one-third were for psychiatric disorders. 'Veterinary medicine in relation to human medicine' includes information, to give some random examples, on salmonella infection in day-old turkey chicks and in sheep and abortion in shepherd's wives, the prevalence of leptospirosis in man, domestic and wild animals in Malaya and the spread of rabies in Europe.

Altogether the Annual has maintained its high standards, but here is one suggestion to the eminent editors. Since many will use the volume to find references to original articles, their task would be lightened if the references given at the end of each section included the author's names in alphabetical order, and even perhaps titles of articles.

Tuberculose Initiale. By FRANCK TISSOT. (Pp. 184; 11 figures. Fr. fr. 1,500.) Paris: Doin. 1956.

This book is a very comprehensive study of tuberculosis in France. Although it claims to be about primary tuberculosis, it inevitably deals to a certain extent with the more serious forms of the disease, particularly as it affects adolescents and young adults. The book covers epidemiology, diagnosis, diagnostic tests, radiology, bronchoscopy and treatment.

There is an interesting chapter on the relationship between infection and resistance, and the author pleads for more world-wide research on these lines. He also includes a long chapter on the psychological aspect of tuberculosis, and of the part that different temperaments play in causing people to succumb to the infection. A seven-year follow-up by Juteau of 175 cases of primary tuberculosis is included. It is interesting to notice that the author includes eight authentic cases of infection occurring after very short contact.

In the section on treatment there is full discussion on the use of antibiotics and cortisone, but Professor Debré's practice of giving drugs to any child who becomes tuberculin positive is evidently not universally accepted in France, and indeed Tissot says many French chest physicians reserve judgment on this matter.

The chapter on surgery in primary disease is very short and the least satisfactory section in the book, which ends with a short chapter on B.C.G.; this, the author feels, is a safe and efficacious procedure, particularly with all the evidence in its favour from mass campaigns since the war.

One gains the impression on reading the book that the French regard primary tuberculosis more seriously than do many chest physicians in this country.

Therapie mit ACTH Cortison und Cortison-Derivaten bei Kinderkrankheiten. By FRITZ SOUCHON. Abstracted from *Archiv für Kinderheilkunde*, Vol. 32. (Pp. viii+109; no figures. 3 tables. DM. 21.—.) Stuttgart: Ferdinand Enke. 1956.

This monograph honours the 70th birthday of Professor Rominger. A brief section on general considerations is followed by a consideration of the use of A.C.T.H. and cortisone and the newer derivatives of cortisone in therapy. The rheumatic conditions, allergies, blood diseases, tumours, kidney affections, endocrine upsets, acute infections, tuberculosis and sarcoidosis are all discussed. The biochemical problems of prematurity and infancy are mentioned, as are some surgical conditions.

Had this monograph been somewhat longer the literature could have been more fully covered; had it not tried to deal with so many subjects in such a short space it might have dealt more thoroughly with some one or other part of its subject matter. As it is, the little bit of everything included necessitates a very curt examination of the many problems involved and it is difficult to know to whom the book should be recommended.

Atlas Hematologiczny, 2nd ed. By W. LAWKOWICZ and I. KRZEMINSKA-LAWKOWICZOWA. (Pp. 283. Zloty 80.—.) Warsaw: PZWL. 1956.

The first edition of this book on haematology was published in 1952 and the advances in this subject have necessitated a further edition after only four years. Having no better insight into the Polish language than knowing the equivalent for 'Good Health', it is difficult for the reviewer to look critically at the text. The colour pictures in this atlas, however, are of a high order and faithfulness of reproduction which makes their contemplation easy and their consultation profitable. The words used in the legends to the pictures are so similar in shape to those to which one is accustomed that, as far as the pictures are concerned, ignorance of the language is no great hindrance.

This book is obviously of much practical interest and could be used for reference and for teaching; the colour pictures are so good, indeed, that it would be nice to know if the text comes up to their standard.

Säuglings-Enteritis. Edited by A. ADAM. (Pp. xii+534; 43 figures. DM. 60.—.) Stuttgart: Georg Thieme Verlag. 1956.

Professor Adam, who in the early 1920s was the first to suggest that certain types of *Escherichia coli* were responsible for epidemic infantile gastro-enteritis, has collaborated with nine authors, each of whom is well recognized as expert in the particular aspect of infantile gastro-enteritis. The book they have produced on this subject is an extensive and comprehensive study and should be a useful reference volume.

The antigenic classification of the specific serological types of *E. coli* is described in detail: the biochemical reactions of the different H antigenic variants of the various serotypes is given, and it is suggested that some of Adam's biotypes were strains of the specific serotypes that are now recognized, although their identity cannot be proved as none of Adam's original cultures has been saved. There is a detailed description of techniques used in Germany for isolating and identifying these serotypes of *E. coli*.

A short chapter deals with the enteritis due to *Salmonellae* and *Shigellae*; most of the infections occurred

amongst those over the age of 5; the heaviest mortality being amongst infants; a description is given of the exudate found in the faeces of a case of dysentery, but there is no mention of how often a similar exudate is found in a salmonella infection.

A very comprehensive chapter contains valuable material and observations on epidemiology of these *E. coli* infections and analyses the work for and against their being the cause of epidemics; there is a review of epidemiological investigations in which the H and the phage typing were employed. As so often happens when many articles are abstracted and described in a small space, some parts of this chapter are not as detailed as might be desirable, and this can confuse the reader. However, the references are accurate and doubtful statements were clarified when the original articles were consulted.

An extremely valuable chapter on the morbid anatomy at necropsy is based on the personal observations of G. Ilgner, who had access to material which is rarely obtained in England, as all of it was fixed within a very few hours of death.

One chapter deals exhaustively with the problems of protein and carbohydrate metabolism and the experiments on amino-acid metabolism are particularly interesting. The formation of biogenic amines is said to be caused by deamination of amino-acids instead of decarboxylation and a few of the references are not listed, which can be irritating; another curious mistake is the description of Aristophanes as a philosopher and attributing to him a saying of Heraklitos.

Adam's own contribution is on the pathogenesis, treatment and clinical presentation of gastro-enteritis, the last of which he explains on anatomical and biochemical findings; he feels that parenteral infections cause some cases, basing part of his argument on what might be a dangerous foundation, that is on negative bacteriological results. In this comprehensive chapter there are details of some types of enteritis seldom, if ever, seen in England, including enteritis necroticans due to *Clostridium welchii*.

The possible paths by which infection can be spread and many techniques to make the manoeuvres for admitting, nursing and handling babies safe, are fully discussed. Although many of the methods are widely used, few now practice a 'napkin round' and many would object to the use of a 1½ % solution of formaldehyde for washing floors.

Ninth International Congress of Paediatrics

The Ninth International Congress of Paediatrics will be held in Montreal, Canada, from Friday, July 19 to Thursday, July 25, 1957, under the chairmanship of Dr. Alan Ross, Professor of Paediatrics, the Montreal Children's Hospital, Montreal 25, Canada.

British Paediatric Association Memorandum on the Use of Radio-iodine in Paediatrics

In 1956 the British Paediatric Association set up a subcommittee to consider the use of radioactive iodine in paediatrics in relation to possible carcinogenic effects. Its members sought advice from Dr. E. E. Pochin, of University College Hospital, and Dr. L. F. Lamerton, of the Physics Department, Institute of Cancer Research, Royal Cancer Hospital, who presented the data and explained the calculations on which the following conclusions are based.

1. That no form of radio-iodine should be used to treat an over-active gland in a child and that therefore the use of radio-iodine for the therapy of thyrotoxicosis did not require discussion.
2. That there appeared to be increased vulnerability to the late effects of external *x*-irradiation with doses of the order of 250 reps, or more, at least up to the age of 6 years, and that there was no evidence of the age at which vulnerability decreased to the adult level.
3. That it was not possible to feel sure that test doses of ^{131}I as low as 1μc might not be hazardous in children.
4. That, bearing in mind that the half-life of ^{131}I was 192 hours and of ^{132}I 2·3 hours, ^{132}I was not likely to be hazardous in test doses of about 4μc, a dose which is adequate for the usual tests which are completed within the first four to six hours, but not for those requiring longer times.
5. That ^{131}I should not be used in children when the employment of ^{132}I would give the information which is needed. In the calculations leading to this conclusion several 'safety factors' are involved which make it doubtful whether any harm will actually result from the use of small doses of ^{131}I, and it must be left to the individual paediatrician to decide whether its use is justifiable in the investigation of any specific clinical problem.

(Signed) D. V. HUBBLE
J. H. HUTCHISON
P. R. EVANS

Correction

We regret that in the paper entitled 'Oesophageal Reconstruction in Children Using Intrathoracic Colon' by Charles D. Sherman and David Waterston (*Archives of Disease in Childhood*, 32, 11) the source of the paper as stated was incorrect; this should have read '*From the Department of Surgery, University of Rochester, New York, and The Hospital for Sick Children, Great Ormond Street, London*'.

THE NEPHROTIC SYNDROME IN EARLY INFANCY:

A REPORT OF THREE CASES*

BY

H. McC. GILES, R. C. B. PUGH, E. M. DARMADY, FAY STRANACK and L. I. WOOLF

From the Department of Paediatrics, St. Mary's Hospital, The Hospital for Sick Children, Great Ormond Street, London, and the Central Laboratory, Portsmouth

(RECEIVED FOR PUBLICATION, DECEMBER 12, 1956)

The nephrotic syndrome is characterized by generalized oedema, hypoproteinaemia with diminution or reversal of the albumin/globulin ratio, hyperlipaemia and gross albuminuria. Haematuria is not prominent; hypertension and azotaemia, except in the terminal stages, are slight and transient and often do not occur at all. Recognition of this syndrome presents no difficulty but in many cases, particularly in childhood, its cause remains obscure. Occasionally certain drugs such as troxidone or mercury, or certain diseases such as amyloidosis, pyelonephritis, diabetes, disseminated lupus erythematosus or renal vein thrombosis, can be incriminated. In cases which develop renal failure and come to necropsy the lesions of glomerulonephritis (Type I or Type II of Ellis, 1942) may be found. Other patients, especially children, may never show any unequivocal features of glomerulonephritis and appear ultimately to make a complete recovery; such cases belong to the group usually classified as lipoid nephrosis, in which the lesions are held to involve predominantly the renal tubules, glomerular damage being slight or absent. However, this condition is relatively uncommon and, by definition, not of itself fatal; descriptions of the morbid anatomy must therefore be based on somewhat limited observation, and the primary cause of the disorder and its relationship to glomerulonephritis are still uncertain.

It is exceedingly rare for the nephrotic syndrome to appear during the first few weeks of life but when this does happen it is reasonable to suggest that the basic disorder may have originated *in utero*. The study of the small group of cases of 'congenital nephrosis' is therefore of particular interest. In the three examples now reported there is, moreover, evidence of genetic aetiology inasmuch as two of the infants were brother and sister and both sets of parents were cousins. Further points of interest were the demonstration of anisotropic crystalline material in alcohol-fixed tissues from all three infants, and the discovery on renal microdissection of lesions of the proximal tubule recalling those found in Fanconi-Lignac disease (cystinosis).

Case Reports

The parents of the first two patients (and the paternal grandparents) are first cousins. They, and a sister born three years before the first of her affected siblings, have been investigated in detail and show no sign of renal disease. There is no history of renal disease in any other member of the family. The pedigree of this family is shown in Fig. 1.

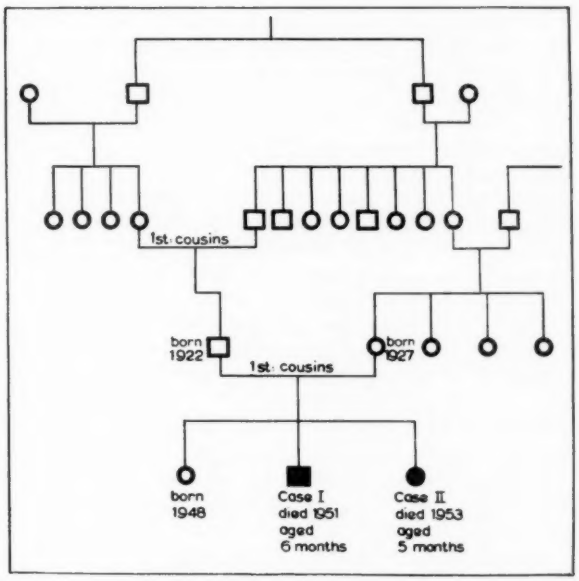

FIG. 1.—Pedigree of Cases 1 and 2.

* Cases 1 and 2 were presented at a meeting of the Pathological Society of Great Britain and Ireland on January 7, 1956, and Cases 1, 2 and 3 at the Annual Meeting of the British Paediatric Association on April 27, 1956.

Case 1. M.R., a full-term male infant weighing 5 lb. 8 oz., was born on May 9, 1951, and was admitted to hospital on September 6, 1951, aged 4 months. At birth his legs had been swollen and from the waist down his skin had a slightly bluish tinge. During the first two weeks of life the swelling and the blueness gradually disappeared. Subsequently, however, there were repeated attacks lasting a day or two in which he passed very little urine and his legs again became tense and swollen; the attacks ended with the passage of much urine and disappearance of the oedema. He had been breast-fed throughout.

On admission he was a pale, rather ill-looking infant with tense pitting oedema of the legs and abdominal wall; there were purpuric spots and blotches in the oedematous regions. The optic discs and retinae were pale but otherwise normal. Blood pressure was 140/90 mm. Hg. A loud systolic murmur was audible over the precordium, maximal at the apex. The abdomen was tense, and ascites was suspected; the left kidney was palpable and thought to be enlarged. The urine contained 250 mg. protein per 100 ml., and the deposit showed 5-10 red cells per high-power field. Haemoglobin was 7·4 g. per 100 ml. and leucocytes 24,100 per c.mm. with 84% polymorphs. The serum cholesterol was 359 mg. per 100 ml., albumin 0·4 g. and globulin 3·21 g. per 100 ml., potassium 3·1 mEq., plasma chloride 100 mEq., bicarbonate 22·5 mEq. per l. and blood urea 26 mg. per 100 ml. The blood Wassermann reaction was negative and a radiograph of the long bones showed no abnormality.

COURSE IN HOSPITAL. Breast feeding was continued after admission. Oedema subsided, slowly at first but more rapidly after a few days with the passage of a number of loose stools, although it did not clear entirely from the legs. The spleen became palpable 3-4 cm. below the costal margin. Following blood transfusion his haemoglobin rose to 14·3 g. per 100 ml. but the cardiac murmur persisted unaltered. During the second week diarrhoea ceased and oedema returned. On September 18 he had a succession of generalized convulsions for which phenobarbitone was given. On the same day he received two injections of 20 ml. each of 25% salt-poor human albumin solution ; there was no subsequent alteration in weight or degree of oedema, but the urinary protein concentration rose to 2 g. per 100 ml. On September 19 serum potassium was 2·8 mEq. per l., calcium 5·6 mg. per 100 ml. and albumin 0·98 g. per 100 ml. Potassium chloride, 1 g. twice daily, and calcium lactate, 1 g. four times daily, were started, and given intermittently for the remainder of the illness. Urea, 1 g. thrice daily, had no diuretic effect.

For the remaining four weeks of life the course was one of alternating oedema, sometimes accompanied by fits, and dehydration associated with diarrhoea. There was no significant azotaemia, blood urea being 32 mg. per 100 ml. three days before death. The blood protein and cholesterol levels and the urinary findings remained typical of the nephrotic syndrome. Hypokalaemia and hypocalcaemia persisted and there was transient hypochloraemia (plasma chloride 80 mEq. per l.). Blood pressure remained about 140/90 mm. Hg. Treatment was directed towards maintaining a reasonable degree of hydration and correcting the various electrolyte disturbances as they occurred. However, the infant did not recover from a final episode of dehydration and died on October 20.

NECROPSY. The necropsy was performed 50 hours after death. The body was that of a male infant in poor general nutritional condition (height 21 in., body weight 7½ lb.) with undue laxity of the skin over the upper part of the body and oedema of the prepuce and the legs below the knees. The fontanelles were patent and depressed.

The middle ears contained a small quantity of slightly blood-stained mucopus. The brain weighed 584 g. and was poorly differentiated and oedematous. On the external surface of the heart there were several small recent subpericardial ecchymoses over the anterior aspect of the right ventricle. The right heart was dilated and the left ventricular wall was of firm consistency and measured 1 cm. in thickness. The anterior portions of both lungs were emphysematous, but posteriorly and in both lower lobes there was congestion and collapse with basal consolidation.

The liver was reduced in weight (150 g. as compared with the expected weight of 200 g.), dull, yellow-brownish and of flabby consistency. It cut easily and the cut surface was swollen, with an ill-defined yellowish coloration at the periphery of the lobules and dark, reddish-brown areas centrally. The gall bladder was small with a thickened fibrous wall and its lumen contained a few small, oval, dark calculi and some whitish mucoid material; one of the calculi was impacted in the cystic duct. The extra-hepatic biliary system was normal. The spleen, which was of average weight, was congested with irregular areas of haemorrhage in the pulp.

The kidneys were of about equal size and were obviously very considerably enlarged. The right weighed 40 g. (expected weight 26 g.) and the left weighed 46 g. (expected weight 25 g.). The appearances were similar in the two and externally the parenchyma appeared paler and flabbier than normal, with some lobation of the surface. The capsules stripped readily and the subcapsular surfaces were very finely granular, with large numbers of raised pale nodules of uniform size distributed evenly on a more congested background. The kidneys cut easily and the cut surfaces were pale. There was marked swelling and widening of the cortices, in which enlarged glomeruli could often be seen as granules. In all parts the cortico-medullary junction zones were blurred. The renal artery was duplicated on both sides. The calyces, pelves and lower urinary tract were entirely normal. Examination of the remaining viscera revealed no significant abnormality.

HISTOLOGY. Tissues were fixed in 10% formol-saline. All sections were stained with haematoxylin and eosin, and by other methods (periodic-acid-Schiff, etc.) as indicated. Small portions of liver, spleen, bone marrow and kidney were also fixed in absolute alcohol and sections were stained with an alcoholic solution of basic fuchsin.

Examination of the formol-saline fixed material revealed significant lesions in the liver and kidneys and confirmed the presence of cerebral oedema and pulmonary congestion and oedema. The consolidated zones at the lung bases were shown to be areas of aspiration pneumonia.

In the liver there was a moderately severe diffuse biliary fibrosis in addition to generalized centrilobular congestion and peripheral fatty infiltration (Fig. 2). The

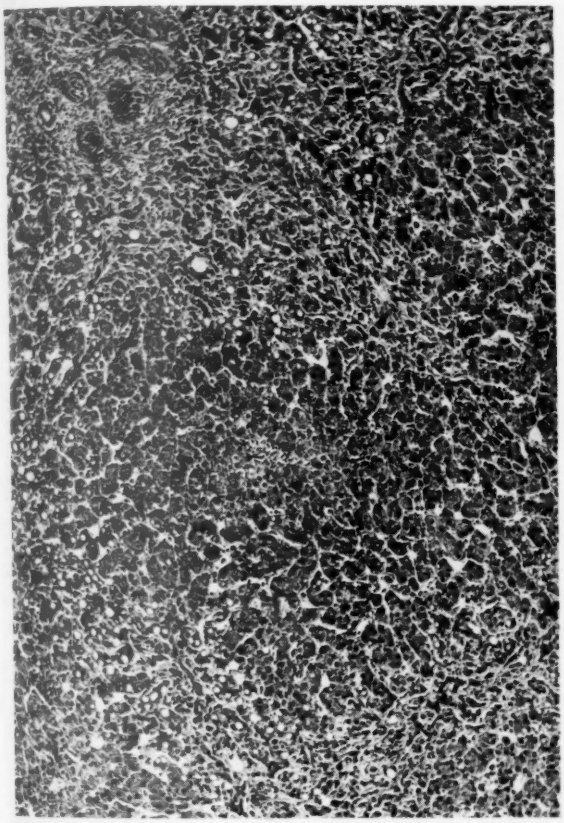

FIG. 2.—Case 1: liver. Diffuse biliary fibrosis with an increased amount of connective tissue in the portal tracts. Haematoxylin and eosin. × 100.

individual lobules were smaller than normal due to proliferation of fibroblastic and fibrous tissues between the portal tracts. The central veins were normal. The perilobular strands contained some proliferated bile ducts, some lymphocytes and plasma cells and many macrophages laden with iron pigment, which was also seen in small amounts in the Kupffer cells, and occasionally within parenchymal liver cells. The liver cells were of normal size, although a few multinucleate forms were seen at the periphery of some lobules. There was no evidence of bile retention within the liver cells, the bile canaliculi, or the bile channels in the portal tracts. In the wall of the gall bladder there were small numbers of chronic inflammatory cells in the submucosa; the mucosa was poorly preserved.

The changes were identical in the two kidneys. The most striking feature was the much greater severity and extent of tubular as compared with glomerular damage (Fig. 3). The glomeruli, however, varied very considerably in size and appearance; some were entirely normal, others were hypertrophied and bulged into the proximal convoluted tubule and many were undergoing ischaemic changes. In these latter there was a variable degree of periglomerular fibrosis as well as some fibrosis of the tuft, associated with irregular thickening of the basement membrane. A few hypertrophied glomeruli showed proliferation of the capsular and glomerular epithelium and increased cellularity due to endothelial proliferation, and here and there small and rather ill-defined epithelial 'crescents' were seen. The periodic-acid-Schiff technique revealed some thickening of the basement membrane in the more central portions of many of the partially ischaemic glomeruli although the peripheral capillary loops were normal. There was no evidence of the glomerular digitation that is such a characteristic feature of Type II nephritis. The tubules were grossly abnormal, the changes being more marked in the cortex than in the medulla. In the cortex there were radially disposed areas of compression, distortion and partial or complete atrophy of the tubules with intervening zones of marked dilatation and hypertrophy. The tubular epithelium varied considerably; in the dilated tubules the cells were flattened and resembled endothelium but in the hypertrophied ones they were plumper and showed all stages of degeneration with cytoplasmic vacuolation, nuclear disintegration and the formation of casts in the lumen. Similar but less regular changes were seen in the medullary tubules. In frozen sections, isotropic sudanophil fat was seen in the lumen and epithelial cells of some of the dilated cortical tubules. In the interstitial tissues there was a diffuse increase of moderately cellular fibroblastic tissue which had a radial arrangement in the cortex corresponding to the areas of maximal tubular damage. Small numbers of chronic inflammatory cells were scattered throughout and there were some zones of partially hyalinized collagen seen here and there (Fig. 4). In the medulla there was a more generalized increase of connective tissue, with fewer inflammatory cells. Vascular changes were not striking and consisted of hypertrophy and, occasionally, hyalinization of the glomerular afferent arterioles, some intimal thickening and elastic reduplication in a number of the intralobular arteries and a little irregular intimal hyperplasia in the main renal vessels. The renal pelvis and lower urinary tract were histologically normal.

Alkaline phosphatase was demonstrated in smaller amounts than normal in the epithelium of the cortical tubules.

Case 2. S.R., a sister of the previous case, was born three weeks prematurely on August 28, 1952 (birth weight 5 lb. 5 oz.), and was admitted to hospital on November 14 at the age of 2½ months.

Except that her mother thought she passed more urine than normal there had been nothing unusual about her progress until four weeks previously when her legs were

FIG. 3.—Case 1: kidney. The glomeruli are normal or enlarged. The tubules are dilated, with epithelial degeneration and atrophy. Haematoxylin and eosin. × 110.

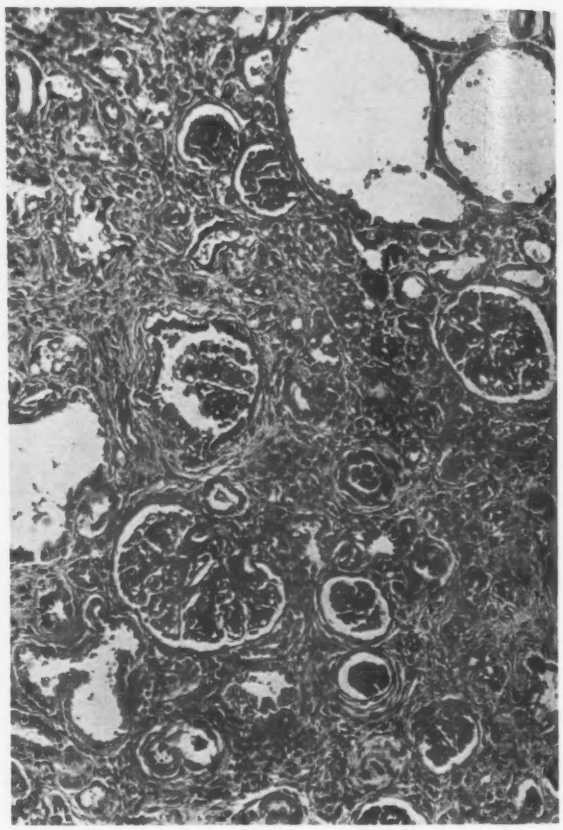

FIG. 4.—Case 1: kidney. Many of the glomeruli are ischaemic and there is irregular tubule dilatation. The interstitial tissues are increased and are denser than normal. Haematoxylin and eosin. × 110.

noticed to be swollen. This swelling had persisted, with some fluctuation in severity.

On admission she was a pale infant with mild pitting oedema of the legs and feet but no other abnormal clinical findings. Her blood pressure was 85/50 mm. Hg; the eye grounds appeared normal. The urine contained 2 g. per 100 ml. of protein and the deposit showed moderate amounts of red cells and some hyaline and granular casts; the specific gravity was 1001. Haemoglobin was 8·7 g. per 100 ml. and leucocytes 5,200 per c. mm. Blood urea was 15 mg. per 100 ml., cholesterol 348 mg., total protein 2·84 g. (albumin 0·7 g., globulin 2·14 g.) plasma chloride 107 mEq. per l., plasma bicarbonate 12·3 mEq., serum sodium 139 mEq. and serum potassium 4·8 mEq.

COURSE IN HOSPITAL. Breast feeding was continued after admission. Heavy proteinuria persisted but the urinary deposit showed only a few red cells; blood pressure never exceeded 95/55 mm. Hg. About December 17, both weight and the degree of oedema began rapidly to increase, and on December 23 feeds of salt-free milk ('lonalac') were substituted for breast milk, and aureomycin, 65 mg. six-hourly, was started as a prophylactic against infection. On December 12, the serum potassium had fallen to 4·3 mEq. per l., and bearing in mind the marked terminal hypokalaemia found in M.R., a dose of 1 g. daily of potassium chloride was started and increased on December 28 to 2 g. daily. On January 7, 1953, oedema began to diminish, and during the subsequent two weeks body weight fell from 11 lb. to 8½ lb. Unfortunately, this loss of fluid was accompanied by a rise in blood urea to 82 mg.per 100 ml. and a deterioration in general condition. On January 23, plasma bicarbonate was 11·7 mEq. per l., chloride 114 mEq., and potassium 3·8 mEq.; intravenous infusions of ⅙ molar sodium lactate solution, ½ strength Hartmann's solution with 2·5% dextrose and blood produced temporary improvement, with a fall in blood urea to 40 mg. per 100 ml. on January 29. During the subsequent week, plasma bicarbonate and serum potassium levels remained low in spite of increasing oral potassium intake to 2·5 g. daily and giving regular ⅙ molar sodium lactate solution. The infant's general condition remained grave and on February 1 her respirations were gasping and her colour poor; she died that day.

NECROPSY. The necropsy was performed 22 hours after death. The body was that of a pale, wasted female infant with a large head, puffy face, distended abdomen

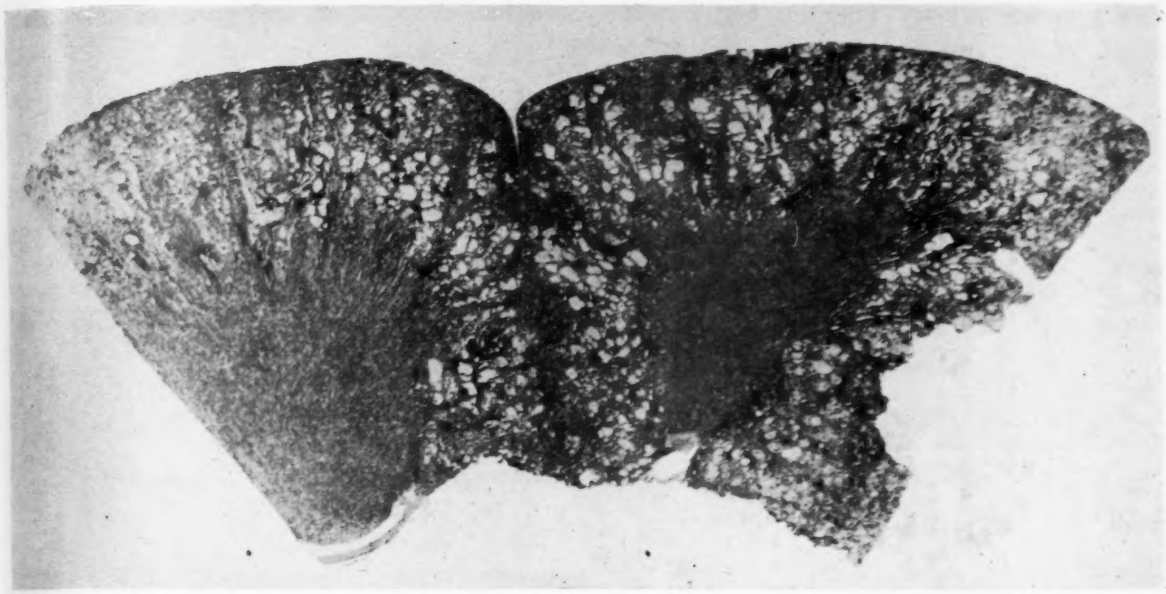

FIG. 5.—Case 2: kidney. Low-power view showing marked dilatation of the cortical tubules. The medulla appears relatively normal. Haematoxylin and eosin. × 5·5.

and pitting oedema of the lower limbs, labia and sacral region (height 20½ in., body weight 9¼ lb.). The cranial sutures were not united and both fontanelles were large and depressed. All the mucous membranes were pale.

The subcutaneous tissues in all parts of the body, as exposed by the routine incisions, contained large amounts of clear oedema fluid. The brain weighed 644 g. (normal for the age) and was oedematous with some simplification of the gyral pattern in the frontal lobes and compensatory dilatation of the anterior horns of the lateral ventricles. The right side of the heart was considerably dilated but the left ventricle was of normal size, its wall measuring 0·8 cm. in thickness. Each pleural cavity contained between 60 and 70 ml. of turbid whitish fluid and the lungs were congested and collapsed but showed no visible or palpable evidence of consolidation. The peritoneal cavity contained 25 ml. of yellowish, slightly cloudy fluid and there was gross gaseous distension of the stomach and large bowel, which appeared to have caused the abdominal enlargement. The liver was increased in weight (224 g. as compared with the expected weight of 188 g.), with centrilobular congestion and some fatty changes at the periphery of the majority of the lobules. The gall bladder and bile ducts were normal. The spleen was enlarged to nearly twice normal and weighed 28 g.; the pulp was intensely congested. The kidneys were very considerably enlarged, the right weighing 60 g. (expected weight 25 g.) and the left 65 g. (expected weight 25 g.). Both showed definite lobation of the surfaces, whilst the capsules stripped readily to reveal pale, finely granular cortices, with some congestion of the stellate veins and many tiny, yellowish elevations upon a darker, brownish-yellow background. The parenchyma cut easily and there was swelling and widening of the cortical tissues, blurring of the cortico-medullary junction zones and some pallor of the medullae. Closer examination of the cortices showed a fine honeycomb pattern, with large numbers of tiny cystic spaces separated by radially disposed strands of swollen parenchyma; no glomeruli could be distinguished (Fig. 5). The calyces, pelves, renal vessels and the lower urinary tract were entirely normal. Examination of the remaining organs revealed no significant changes.

HISTOLOGY. Tissues were fixed in 10% formol-saline. All sections were stained with haematoxylin and eosin as a routine and by other methods as indicated. As in Case 1, portions of liver, spleen, bone marrow and kidney were fixed in absolute alcohol and sections were stained with an alcoholic solution of basic fuchsin.

In the formol-saline fixed material very striking lesions were seen in the kidneys, and the macroscopic findings were confirmed in the other organs. There was no increase of connective tissue in the liver, such as was seen in Case 1. An incidental finding of no relevance in the present context was a number of intranuclear and intracytoplasmic inclusions, characteristic of cytomegalic inclusion disease, in the epithelial cells of the ducts of one of the submandibular salivary glands.

Identical lesions were seen in the two kidneys and, as in Case 1, the tubules were more seriously affected than the glomeruli. Moreover, comparison of the two cases showed that the same basic lesion was present in both infants, although it was in a more advanced stage in Case 1. In the present case, the lesions were almost entirely cortical in situation, the only relevant changes in the medulla being vascular congestion, prominence of and increase in the amount of interstitial tissue, and some irregular and slight dilatation of a number of the tubules in the boundary zone. The majority of the glomeruli were of normal size and appearance, although a few were

FIG. 6.—Case 2: kidney. The glomeruli vary in size and are separated by greatly dilated tubules. Haematoxylin and eosin. × 110.

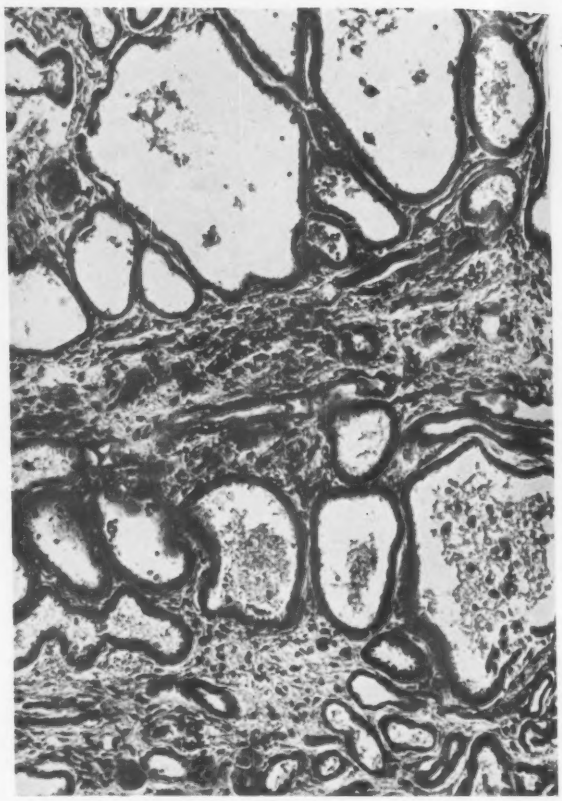

FIG. 7.—Case 2: kidney. The tubules are grossly dilated and separated by oedematous fibroblastic tissue. Haematoxylin and eosin. × 110.

hypertrophied and some, especially in those parts of the kidney where there had been proliferation of the interstitial tissues, showed a variable amount of periglomerular fibrosis and fibrosis of the capillary tuft (Fig. 6). A very few of the cortical tubules were of normal size and appearance, but more commonly there was marked degenerative change in the epithelium, with considerable dilatation of the tubule lumen and flattening or hyperplasia of the lining cells, and with marked vacuolation, cloudy swelling or hyaline droplet degeneration of the epithelium. The dilated cortical tubules were found to correspond exactly with the cystic spaces noted on naked-eye examination. Many tubules, and especially those that were dilated, contained varying proportions of red blood cells, structureless eosinophil casts, desquamated epithelial cells and granular debris in their lumina. Frozen sections showed a small amount of isotropic fat in some of the hypertrophied tubules and small focal collections of fat-laden macrophages interstitially. Throughout the cortex there was a diffuse increase of rather loose fibroblastic tissue (Fig. 7) which tended to have a radial arrangement and was infiltrated with small focal collections of chronic inflammatory cells. The intra- and extra-renal branches of the renal artery were normal and no abnormality could be found in the calyces, pelves and lower urinary tract.

Alkaline phosphatase was present in the cortical tubules but, as in Case 1, in reduced amount.

Case 3. The parents of the third patient are second cousins once removed. Twins, born four and a half years before the patient, are well and apparently normal, as are the parents; the mother has had one miscarriage. There is no family history of renal disease. It has unfortunately been impossible to obtain a full pedigree.

The patient, S.W., was born at term on November 19, 1952, weighing 6 lb. 10oz. He was breast-fed, but sucked poorly and lost weight steadily. He was admitted to hospital on December 14, 1952, aged 3½ weeks, because of failure to thrive. He was then a thin, miserable infant weighing 5 lb., with blood pressure 75/? mm. Hg. There were no other abnormal clinical findings.

COURSE IN HOSPITAL. On December 17, his urine contained protein, 40 mg.%, the deposit showed 20-30 pus cells per high-power field, with an occasional red blood cell, and culture yielded a light growth of coliforms and *Proteus*. Haemoglobin was 12 g. per 100 ml., leucocyte count 22,100 per c. mm., of which 73% were polymorphs, and blood urea 112 mg. per 100 ml. Because of the leucocytosis, a spike of fever up to 100° F. and the onset of paronychia, a course of penicillin was started. On December 20, chloramphenicol was substituted for

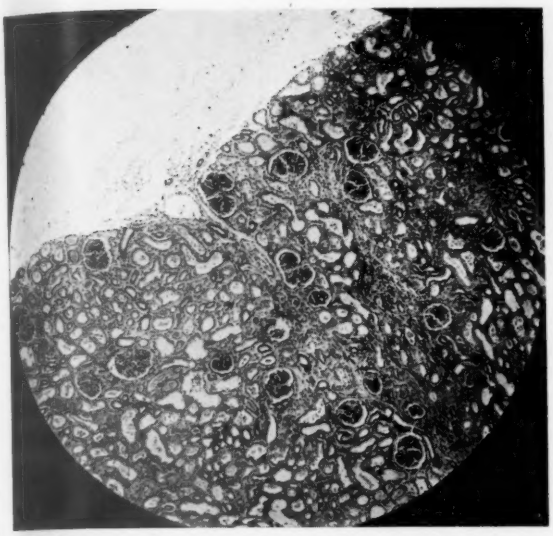

FIG. 8.—Case 3: kidney. Low-power view showing irregularly dilated cortical tubules and normal-looking glomeruli. Haematoxylin and eosin. × 50.

penicillin and was continued for four days. By December 23, blood urea had fallen to 65 mg. per 100 ml., and by December 29 to 34 mg. per 100 ml. On January 7, 1953, however, the urine contained 1,400 mg. per 100 ml. of protein; the deposit showed 4-5 red blood cells per high-power field and culture was sterile. On January 12, urinary protein was 4,000 mg. per 100 ml. and large numbers of red blood cells were seen in the deposit; blood urea was 40 mg. per 100 ml., serum albumin 1·65 g., globulin 2·59 g., cholesterol 291 mg. and phosphorus 7·8 mg. per 100 ml. In view of these findings and the development of oedema, it was felt that the infant should be treated as a case of the nephrotic syndrome, and his diet was changed from expressed breast milk to a synthetic low-sodium milk. The oedema stopped increasing, but there was no improvement in his general condition and he took feeds very poorly. On February 1 he developed rapid grunting respirations, passed some loose stools and looked very pale. The liver was palpable two finger-breadths below the costal margin, and both kidneys were palpable and felt enlarged and hard. Haemoglobin was 4·5 g. per 100 ml., blood urea 72 mg., serum potassium 3·2 mEq. per l. and plasma bicarbonate 5·4 mEq. per l. The urine contained protein, 2,400 mg. per 100 ml., and moderate numbers of red and white blood cells. He was given a blood transfusion of 120 ml. and an attempt was made to correct the electrolyte disturbance with appropriate intravenous fluids. In spite of this his condition deteriorated, he became increasingly oedematous and oliguric, and died on February 3.

NECROPSY. The necropsy was performed seven and a half hours after death. The body was that of a male infant in rather poor general nutritional condition with gross facial oedema, especially in the periorbital regions, and moderate to gross oedema of the upper and lower limbs, the scrotum and of the soft tissue at the base of the neck. The abdomen was distended, with eversion of the umbilicus. Height was 21 in. and body weight 8 lb.

The brain weighed 536 g. (as compared with the expected weight of 516 g.) and was congested and oedematous with flattened convolutions. The myocardium was firm but not hypertrophied. The right pleural cavity contained 5-10 ml. of straw-coloured fluid, both lungs were moderately oedematous and there was some emphysema anteriorly in the right upper and middle lobes. The peritoneal cavity contained 10-15 ml. of straw-coloured fluid and the retroperitoneal tissues were oedematous. The liver was very slightly increased in weight (148 g. as compared with the expected weight of 140 g.) and congested. The gall bladder and bile ducts were normal. The spleen was deeply congested.

The kidneys, ureters and bladder were removed *in toto* and the kidneys were not weighed, although they both appeared to be moderately enlarged. The left kidney was slightly larger than the right and there was some dilatation of the right ureter, pelvis and calyces with compression and thinning of the kidney tissue on that side. The capsules stripped with a little difficulty from both kidneys and the subcapsular surfaces were irregular with many fine yellowish-brown nodules and some congested depressed areas. On the cut surfaces many irregular, radially disposed striae of bright yellow colour were seen in the cortex. The lower urinary tract was normal. There was irregular mucosal congestion throughout the intestine.

HISTOLOGY. Tissues were fixed in 10% formol-saline. All sections were stained with haematoxylin and eosin as a routine and by other methods as indicated. As in Cases 1 and 2 portions of liver, spleen, bone marrow, lymph nodes and kidneys were fixed in absolute alcohol and sections were subsequently stained with an alcoholic solution of basic fuchsin.

In the formol-saline-fixed material significant lesions were found in the bowel and kidneys and the naked-eye findings were confirmed in the remaining organs. In the lower oesophagus there was an extensive acute oesophagitis with congestion, inflammatory cell infiltration and patchy mucosal ulceration. Throughout the small and large intestines the submucosa contained an increased number of pleomorphic inflammatory cells.

The changes in the two kidneys were essentially the same. There were a few small, wedge-shaped foci of chronic pyelonephritic scarring but the most significant abnormality was a marked irregular dilatation of the tubules throughout the cortex and sometimes in the outer medulla as well. By contrast the glomeruli, except in the pyelonephritic scars, were entirely normal for a child of this age (Fig. 8). The dilated cortical tubules (Fig. 9) were lined by a low, flattened type of epithelium which was often irregularly vacuolated and, in frozen sections, was found to contain considerable amounts of isotropic sudanophil fat. The lumina contained desquamated epithelial cells and debris. There was no appreciable increase in the interstitial connective tissues except in the wedge-shaped areas of scarring. Here and there, however, the interstitial tissues contained a little iron pigment,

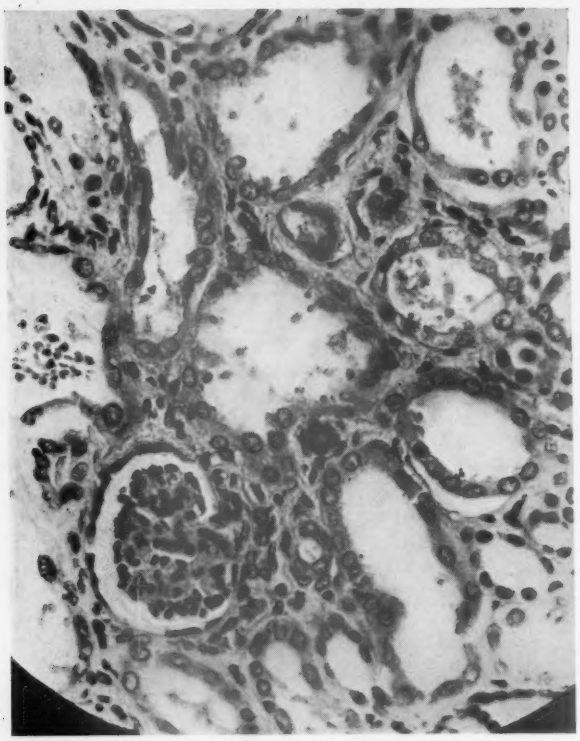

FIG. 9.—Case 3: kidney. Shows a single normal glomerulus surrounded by partially necrotic and dilated tubules. Haematoxylin and eosin. × 300.

FIG. 10.—Case 1: liver. Photographed under partially polarized light; the crystalline material is clearly visible. Alcohol fixed, stained with basic fuchsin. × 60.

small collections of haemopoietic cells and focal aggregates of calcified material in the cortex and boundary zone (nephrocalcinosis). The renal vessels and their branches were normal. The renal lesions in this case resembled very closely those seen in Cases 1 and 2 although they were in a less advanced stage ; in addition there was evidence of a co-existing chronic pyelonephritis and nephrocalcinosis.

Special Studies

Examination of the Alcohol-fixed Tissues. The alcohol-fixed portions of liver, bone marrow, spleen and kidney from each infant were stained with alcoholic basic fuchsin. In Case 1 faintly bluish, unstained, doubly refractile crystalline material was found in all four tissues. The crystals were of a roughly square shape, measuring approximately 5μ × 5μ, and were soluble in water, dilute acids, ammonia and aqueous formaldehyde. They occurred in greatest concentration in the liver, where they were found most frequently within the hepatic cells, but were also seen in the Kupffer cells, and occasionally in the portal tracts (Fig. 10). Small numbers were present in macrophages in the marrow and spleen. An occasional crystal lay, apparently extracellularly, in the interstitial tissues of the kidney. *X*-ray crystallography confirmed the crystalline nature of the material but attempts at exact identification were inconclusive because of the low concentration in the tissues. However, the substance with solubilities and *x*-ray crystallographic properties closest to those observed is cystine.

In Cases 2 and 3 occasional doubly-refractile crystals were seen in alcohol-fixed material from bone marrow, spleen, liver and kidneys. The crystals were similar to those seen in Case 1 but were present in such small amount that positive identification was again impossible.

Paper Chromatography of Blood and Urine. Random post-prandial samples of blood and urine from each case were examined for amino-acids and sugars, using the methods described by Woolf (1951) and Woolf and Giles (1956). The results are summarized in Table 1. Two specimens of urine from Mr. R. and one each from Mrs. R. and L.R. (respectively father, mother and sister of Cases 1 and 2) were similarly examined; all were protein-free and showed no excess of amino-acids or sugars.

Microdissection of Kidneys. Microdissection of the kidneys was hampered in all cases by a moderate amount of irregularly distributed interstitial fibrous tissue. The changes in Cases 1 and 2 were essentially the same (Fig. 11). The glomeruli were normal. The first part of the proximal tubule was replaced by a long and narrow neck lined by thin and flattened epithelium for about the first third of its course. The remainder of the proximal tubule was ballooned in many areas, and considerably

TABLE 1
PAPER CHROMATOGRAPHY OF URINE AND BLOOD

Subject	Material	Date	Creatinine (mg/100 ml.)	Chromatographic Findings
Case 1 (M.R.)	Urine	6.10.51	28	Proline, leucine, valine, taurine ++. Other amino-acids +. Glucose 200 mg. per 100 ml.
	Urine	12.10.51	23	Ethanolamine, β-amino-isobutyric acid ++. Leucine, phenylalanine, tyrosine +. Other amino-acids normal.
	Blood	12.10.51	—	Leucine, phenylalanine +. Other amino-acids normal.
Case 2 (S.R.)	Urine	15.11.52	7	No excess amino-acids or sugars
	Urine	21.11.52	21	No excess amino-acids or sugars
	Urine	12.12.52	20	Ethanolamine ++. Taurine, β-amino-isobutyric acid, +. Sugars normal. Other amino-acids normal
	Urine	10.1 53	37	Ethanolamine, β-amino-isobutyric acid, leucine, valine +. Sugars normal. Other amino-acids normal
	Urine (post-mortem specimen)	1.2.53	18	Leucine, valine, proline ++. Other amino-acids +. Glucose 37 mg. per 100 ml.
	Blood	12.12.52	—	Ethanolamine, taurine, β-amino-isobutyric acid +. Other amino-acids normal
	Blood (post-mortem specimen)	1.2.53	—	General increase in amino-acid levels
Case 3 (S.W.)	Urine	12.1.53	30	No excess amino-acids or sugars
	Urine	2.2.53	18	Leucine ++ β-amino-isobutyric acid, valine +. Other amino-acids normal
	Blood (post-mortem specimen)	3.2.53	—	No excess amino-acids

+ Indicates a moderate, ++ a marked increase over the normal concentration.

wider than normal. The lumen of the tubule was dilated throughout its course, and the epithelium flattened and irregular and in places vacuolated. The ballooning of the proximal tubule was much more advanced in Case 1 than in Case 2. The loops of Henle were normal but in the distal tubules the lumen was dilated, and the epithelium flattened. The collecting tubules were normal.

In Case 3, the changes were somewhat different in that the nephrons were of two types. In the first type the changes were similar to those seen in Cases 1 and 2 exc pt that the narrowing and thinness of the first part of the proximal tubule was less in degree and extent, and the ballooning of the remainder of the tubule less apparent. The overall width of the proximal tubule was in fact normal for an infant of this age but the lumen was dilated and the epithelium flattened. In the second type (Fig. 12) the proximal tubule was similar to that seen in premature infants, that is to say, it was shorter than normal and lacked convolutions. It showed a slight narrowing of the neck for a short distance but the proximal tubule was of uniform diameter throughout. The loops of Henle were normal in both types but the distal tubules showed epithelial flattening and dilatation of the lumen.

Discussion

Nephrotic Syndrome in the Newborn. The nephrotic syndrome is remarkably uncommon during the first few months of life and indeed during the first year; thus in the large and well-documented series of 208 cases reported by Barness, Moll and Janeway (1950), although precise figures are not quoted, the graph showing age at onset indicates only one case aged less than 12 months. Other series (Block, Jackson, Stearns and Butsch, 1948; Galán, 1949) similarly include very few cases in infants. This almost complete immunity in the first year is the more striking in that the second to fourth years are the period of maximum incidence.

The first published account of the nephrotic syndrome in the neonatal period seems to be that of Gautier and Miville (1942). This infant had facial oedema at birth, at 17 days showed marked generalized oedema, and died three days later. No necropsy was obtained. There were no siblings; the mother had been pregnant once before but the embryo died at 6 weeks.

Fanconi, Kousmine and Frischknecht (1951) reviewed the problem of congenital and familial nephrosis and described a family of five siblings, three of whom developed nephrotic symptoms at 4, 10 and 24 days. All these babies died, but in only one, who died in uraemia at $2\frac{3}{4}$ years, was a complete necropsy obtained. In this case the kidneys showed glomerular hyalinization and epithelial crescents, periglomerular lymphocytic infiltration, and atrophy or striking dilatation of the tubules; the liver was fatty.

Eiben, Kleinerman and Cline (1954) reported the case of a premature baby who was oedematous from the sixth day of life and died at 15 weeks. Glomerular changes were relatively slight but there was some periglomerular fibrosis and fibrosis of the tufts with irregular basement membrane thickening. The renal tubules showed considerable dilatation and hypertrophy with epithelial degeneration; they contained small amounts of lipoid, and alkaline phosphatase was present. Changes of benign

FIG. 11.—Case 1: microdissected nephron. Phase-contrast mosaic shows that the glomerulus is joined to the proximal tubule by a narrow neck, the epithelium of which is regular. The remainder of the proximal tubule is distended and ballooned, with flattening of the epithelium. Case 2 shows similar changes. × 200.

FIG. 12.—Case 3: microdissected nephron. Phase-contrast mosaic showing a premature type of nephron. The glomerulus is joined to the proximal tubule by a short narrow neck; the proximal tubule is shorter than normal, lacks convolutions and is reduced in width. × 140.

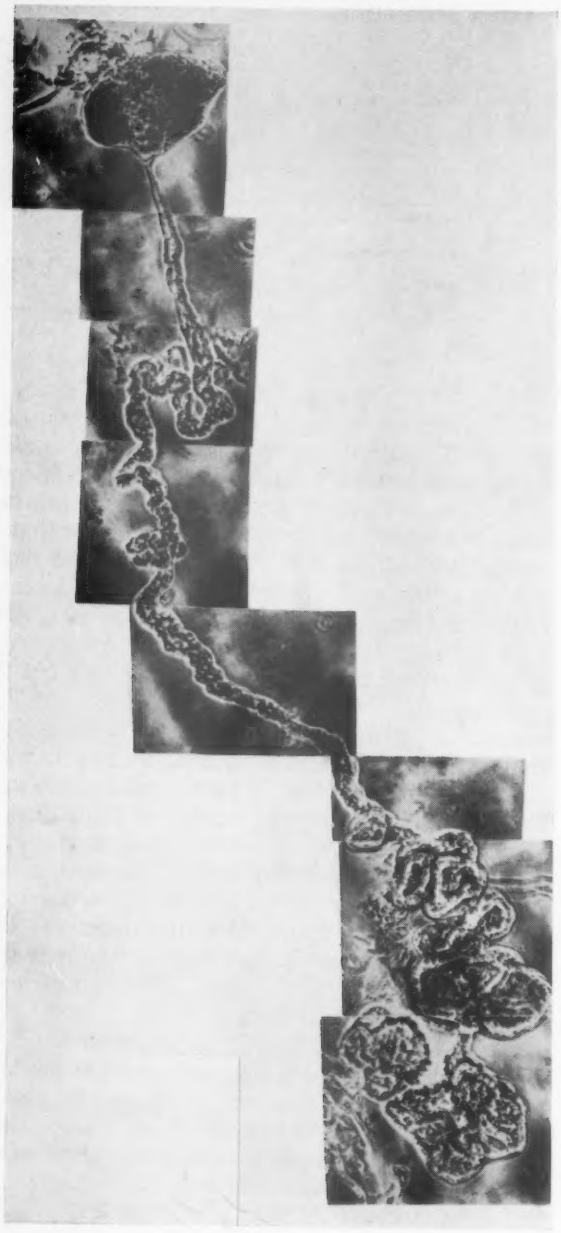

FIG. 11.

FIG. 12.

TABLE 2

NEPHROTIC SYNDROME IN EARLY INFANCY

Author	Sex	Premature	Age at Onset (days)	Age at Death (weeks)	Healthy Siblings	Necropsy Diagnosis
Gautier and Miville (1942)	F.	No	Birth	3	0	—
Fanconi *et al.* (1951)	M	?	24	7	2	No histology
	M	?	10	26		—
	M	No	4	2¾ years		Glomerulonephritis
Eiben *et al.* (1954)	M	Yes	6	15	5	Lipoid nephrosis
Kunstadter and Rosenblum (1954)	M	Yes	9	10	4	Glomerulonephritis
Frischknecht *et al.* (1954)	F	Yes	? Birth	15	3	Glomerulonephritis
Hallman *et al.* (1956) (8 cases)	5M	7 premature	Birth-31	1-44	7 (3 families)	6 Glomerulonephritis
	3F					2 Lipoid nephrosis
Hudson (1956)	F	? No	21	5	0	'Nephrosis'
	M	? No	42	32		'Nephrosis'
Dobbs and France (1956)	M	Yes	Birth	7	2	Congenital 'nephrosis'
Present series	M	No	Birth	24	1	Congenital 'nephrosis'
	F	Yes	40	17		Congenital 'nephrosis'
	M	No	? Birth	11	2	Congenital 'nephrosis'

hypertension were present in the blood vessels. The gall bladder contained several soft black calculi and a single similar calculus lay in the cystic duct. This patient had five healthy siblings.

Kunstadter and Rosenblum (1954) also observed a premature infant who became oedematous on the ninth day and died at 10 weeks. Microscopically the kidneys showed swollen and hyperaemic glomeruli with proliferation of Bowman's capsule and degeneration of tubular lining cells. There were four healthy siblings.

Frischknecht, Zollinger and Keiser (1954) described a further case, again a three weeks' premature infant, who was noticed to be oedematous almost immediately after birth, and died at 3½ months. Slight but definite inflammatory changes were found in the glomeruli, including thickening and splitting of the basement membrane; some of the tubules were dilated and hypertrophied, others atrophied. The patient had three healthy siblings.

Hallman, Hjelt and Ahvenainen (1956) have recently presented a group of eight infants who developed the nephrotic syndrome within the first few weeks of life. Seven of these were premature; all died, their ages at death ranging from 7 days to 10 months. Full pathological details are not yet available but six cases were classified as glomerulonephritis and two as lipoid nephrosis. Three of the infants had one or more healthy siblings; five (including two of the three with healthy siblings) had siblings who were born prematurely and died.

Hudson (1956) encountered two siblings who developed the disorder at 3 weeks and 7 weeks, and died at 5 weeks and 7½ months respectively. The infants were mature by dates, although their birth weights were only 4½ lb. and 5½ lb. The parents were healthy and not consanguineous; they had no other children. The renal lesions in both cases were thought to resemble those of the present series.

Dobbs and France (1956) observed a three weeks' premature infant who was noticed to be oedematous within a few hours of birth and died at 7 weeks. The patient had two healthy siblings; there was no parental consanguinity. The kidneys showed a remarkable degree of tubular dilatation; the majority of the glomeruli were normal, although a few showed pericapsular fibrosis with occasional slight capsular proliferation.

These case reports are summarized in Table 2, which also includes the diagnoses submitted by the respective authors.

Other accounts have been published of various clinico-pathological syndromes associated with renal disease in the neonatal period (Mitchell, 1930; Collins, 1954; Lapage, 1932) but these do not in general provide sufficient clinical and biochemical information for full classification.

Familial Incidence of Nephrotic Syndrome. The familial occurrence of renal disease has frequently been observed (Mitchell, 1930) but in most cases it is impossible to be certain of the exact nature of the disorder. There are few reports of a well-defined nephrotic syndrome occurring more than once in a family. Blechmann (1934) observed two brothers, both of whom developed 'lipoid nephrosis' at 4 years. The first died less than a month from onset; the second recovered. Forge (1950) reported four cases in male and female sets of uniovular twins. In the female set the age at onset was 18 years in both twins, in the male set 13 and 17 years respectively. The 13-year-old died two years later; the outcome in the remaining three cases was not certainly known. Prader (1950) observed a further set of male uniovular twins, both of whom became

ill at 15 years and both of whom died. Goettsch (1948) only once encountered nephrosis in siblings. Fanconi *et al.* (1951) reported the family already referred to, another in which two brothers developed the disease at 3½ years and 6 years, surviving eight months and three months respectively, and a third family in which a sister and brother became ill at 9 years and 14 years, both eventually recovering. As already mentioned, Hudson (1956) observed the disease in a brother and sister. Except in Hudson's cases and one case of Fanconi's no necropsy findings were recorded. Parental consanguinity was not demonstrated in any of the families.

Classification of Present Cases. It seems almost certain that the three cases described in the present report all suffered from the same basic disorder. This view is based on the uniformity of the morbid anatomical changes, the presence of anisotropic crystalline deposits in tissues from all three infants, the demonstration of broadly similar abnormalities in the microdissected nephrons and, in two of the cases, the sibling relationship. There are, however, quantitative histological differences, the changes being most advanced in Case 1 and least advanced in Case 3. This may well reflect the duration of the illness, since the ages at death were 5½, 4 and 2 months in Cases 1, 2 and 3 respectively.

In none of the cases are the classical changes of Ellis Type I or Type II nephritis seen. In Case 1, some basement membrane thickening is demonstrable with the periodic-acid-Schiff technique, but the lesion, although similar to that found in Type II nephritis, is not so diffuse. Moreover, the pattern of the interstitial proliferation is unlike that seen in Type II nephritis and the changes are almost certainly of ischaemic origin. There is no evidence that hypertension *per se* has produced any changes in the kidney. The relative paucity of inflammatory cells in the renal parenchyma is a striking feature of all three cases, and pyelonephritis is clearly not the primary disease. The tubular lesions, comprising atrophy, hypertrophy with dilatation, and epithelial degeneration, are very much more marked throughout than the glomerular changes, and it is postulated that there is a primary tubular lesion which has resulted in proliferation of the interstitial tissues, which in turn has had a secondary strangulating effect upon the glomeruli. This concept is supported by consideration of the ages at which the children died, and by comparison of the renal lesions which show, in Case 1, interstitial collagen and quite severe glomerular sclerosis, in Case 2, fibroblastic interstitial proliferation and only minimal glomerular sclerosis, and in Case 3, no increase in the interstitial tissues, except in the wedges of pyelonephritic scarring, and normal glomeruli.

In summary, the renal changes are thought to be consistent with a 'nephrosis', using the term in the sense of a primary tubular disorder with secondary and relatively minor glomerular lesions. The absence from the kidneys of significant deposits of anisotropic fat would, however, seem to make the qualification 'lipoid' not strictly appropriate.

Unfortunately, chemical analysis of the biliary calculi found in the gall bladder of Case 1 was not carried out. In appearance they were more like pigment than cholesterol calculi. It seems probable that the biliary cirrhosis was due to intermittent calculous obstruction of the large bile passages. Whether these hepatic and biliary lesions are coincidental is unknown. There is no obvious basis for associating them with the renal disease, but the occurrence of gallstones in the closely similar case of Eiben *et al.* (1954) raises the possibility that there is more than a chance relationship.

Genetic Aspects. It is impossible to pinpoint the date of onset of nephrosis and we cannot state categorically that the cases now reported were truly congenital. However, there are reasonable grounds for accepting them as such. Thus, in Case 1 oedema was present at birth; in Case 2 oedema was not noticed until the age of 6 weeks, but by this time the nephrotic syndrome was fully developed, and must have begun much earlier; in Case 3, although again nephrosis was not confirmed until the baby was 7 weeks old, he had been ill since birth. In no instance was there anything unusual about the mother's health during pregnancy, and no extraneous cause for the infant's illness could be found. In such circumstances it is logical to consider a genetic aetiology. In fact, inheritance of a Mendelian recessive characteristic would well explain the occurrence of a disorder, of extreme rarity in the neonatal period, in two newborn siblings (Cases 1 and 2) whose parents are first cousins and in whose family there is no history of renal disease. This hypothesis is strengthened by the existence of a cousin relationship between the parents of Case 3.

Anisotropic Crystalline Material. The significance of this finding is difficult to assess. It is unfortunate that the material could not be positively identified; no more can be said than that it was very possibly cystine. No similar crystals have been found in appropriately fixed and stained tissues of children dying from glomerulonephritis or from causes unrelated to renal disease, but we cannot say

whether or not such crystals may be present in the tissues of children with lipoid nephrosis until further cases have been studied.

Chromatographic Studies. An increased urinary amino-acid concentration was found at one time or another in all three cases. This accords with the observations of Woolf and Giles (1956) who described two types of abnormal urinary amino-acid pattern in the nephrotic syndrome. The first of these, characterized by increased excretion of ethanolamine, β-amino-isobutyric acid and other amino compounds, suggested a disturbance of intermediary amino-acid metabolism. The second type, approximating to that of normal blood and associated with glycosuria, and with azotaemia, hypertension or other evidence of renal failure, was attributed to renal tubular insufficiency, Among the present cases, this latter pattern was found only in the post-mortem urine specimen from Case 2 and in one ante-mortem specimen from Case 1; these were also the only samples containing an increased concentration of glucose. The remaining specimens from all three cases either showed the first pattern or were within normal limits.

Both patterns differ from those of cystine storage disease in their variability, in the presence of increased amounts of ethanolamine, β-amino-isobutyric acid and taurine, and in the absence from the majority of specimens of significant amounts of glucose. The relatively high urinary creatinine concentration found at least once in all of the cases is a further point of distinction from cystine storage disease, in which the creatinine rarely rises above 20 mg. per 100 ml.

We are unable to draw any conclusions from the amino-acid patterns found in the blood of Cases 1 and 3. In Case 2, the pattern found during life resembled that sometimes seen in the nephrotic syndrome in older children (Woolf and Giles, 1956).

Significance of Changes on Renal Microdissection. The similarity of the lesions to those previously described by some of us (Clay, Darmady and Hawkins, 1953; Darmady, 1954; Darmady and Stranack, 1955) in Fanconi-Lignac disease (cystinosis) is of interest. The principal difference would seem to be in the lower end of the proximal tubule, for in Fanconi-Lignac disease ballooning and dilatation of the lumen of the lower part of the proximal tubule have not been a feature in the cases so far examined. It is possible that the anatomical abnormality of the proximal tubule may be due to the genetic linkage of the families concerned, since this is apparent in Fanconi-Lignac disease also. Nevertheless the obvious differences in glycosuria, amino-aciduria and proteinuria correlate more closely with a specific reabsorptive tubular defect, and cannot be attributed entirely to the less specific micro-anatomical lesion. It is therefore probable that the genetic linkage affects the specific reabsorptive enzymes as well as the development of the proximal tubule. The persistence of the foetal type nephrons in Case 3 may not be of significance, for examination of kidneys of normal infants show that foetal nephrons can be found in small numbers in infants up to 8 months. This finding has also been confirmed by Peter (1927).

Aetiology of Congenital Nephrosis. A review of the reported cases of the nephrotic syndrome in newborns shows that apart from the essential clinical and biochemical similarities, the most notable common features are an invariably fatal outcome, usually within the first six months and, as pointed out by Hallman (1956), an association with prematurity. Somewhat unexpectedly, the underlying pathology is almost as heterogeneous as in older children and adults. However, the cases of Eiben *et al.* (1954), of Dobbs and France (1956) and of Hudson (1956) do show renal changes closely resembling those found in the present group. Hudson's cases were also familial, but in the others the familial incidence and genetic background are missing, nor were the tissues examined for crystalline deposits or by microdissection. The diagnosis made by Eiben *et al.* (1954) was lipoid nephrosis, and although the authors could advance no explanation for such an early onset, they believed it unlikely that there could have been an antecedent acute nephritis and felt that this argued for the existence of lipoid nephrosis as an independent entity. Frischknecht *et al.* (1954) interpreted their case as one of intracapillary glomerulonephritis, and attributed the incompleteness of the histological picture to inadequate antibody production in the young infant.

As already indicated, there are occasional references in the literature to the occurrence of the nephrotic syndrome in siblings; but most of these concern older children. Parental consanguinity has not previously been described. There has therefore been little evidence hitherto for a genetic aetiology in neonatal nephrosis. In the cases presented in this report, however, there is strong evidence for such aetiology; and the inherited defect may be manifested by an anomaly of the renal tubules and by the deposition in certain tissues of anisotropic crystalline material.

It is evident from these findings that any attempt at differentiation and classification of neonatal nephrosis demands the most detailed study and the use of every appropriate investigative technique.

Summary

The cases are reported of three infants who manifested the nephrotic syndrome at or within a few weeks of birth and died before the age of 6 months. Two of the cases were siblings whose parents were first cousins; the parents of the third case were also cousins. Each case showed (i) a similar abnormality of the renal tubules on microdissection; (ii) doubly refractile crystalline material in alcohol-fixed tissues; (iii) predominant lesions in the renal tubules, glomerular damage being minor and probably secondary. The severity of the histological changes could be correlated with the presumptive duration of the illness. These findings suggest that all three infants suffered from the same, and probably genetically determined, primary disorder.

Other reported cases of neonatal nephrosis show differing morbid anatomical patterns but have had a uniformly fatal outcome.

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References

Barness, L. A., Moll, G. H. and Janeway, C. A. (1950). *Pediatrics*, 5, 486.
Blechmann, G. (1934). *Bull. Soc. Pédiat. Paris*, 32, 362.
Block, W. M., Jackson, R. L., Stearns, G. and Butsch, M.P. (1948). *Pediatrics*, 1, 733.
Clay, R. D., Darmady, E. M. and Hawkins, M. (1953). *J. Path. Bact.*, 65, 551.
Collins, R. D. (1954). *Amer. J. Dis. Child.*, 87, 478.
Darmady, E. M. (1954). In *The Kidney*, Ciba Foundation Symposium edited by A. A. G. Lewis and G. E. W. Wolstenholme; London.
——— and Stranack, F. (1955). *Proc. roy. Soc. Med.*, 48, 781.
Dobbs, R. H. and France N. E. (1956). Personal communication.
Eiben, R. M., Kleinerman, J. and Cline, J. C. (1954). *J. Pediat.*, 44, 195.
Ellis, A. (1942). *Lancet*, 1, 1.
Fanconi, G., Kousmine, C. and Frischknecht, W. (1951). *Helv. paediat. Acta*, 6, 199
Forge, J.-F. (1950). *Bull. Soc. Méd. Paris*, 154, 87.
Frischknecht, W., Zollinger, H. U. and Keiser, G. (1954). *Helv. paediat. Acta*, 9, 511.
Galán, E. (1949). *Amer. J. Dis. Child.*, 77, 328.
Gautier, P. and Miville, D. (1942). *Rev. méd. Suisse rom.*, 62, 740.
Goettsch, E. (1948). Brennemann's *Practice of Pediatrics*, vol. 3 ch. 28, p. 14. Hagerstown.
Hallman, N. (1956). Personal communication.
——, Hjelt, L. and Ahvenainen, E. K. (1956). *VIIIth International Congress of Paediatrics, Copenhagen: Exhibition*, p. 74 [E.134].
Hudson, F. P. (1956). Personal communication.
Kunstadter, R. H. and Rosenblum, L. (1954). *Amer. J. Dis. Child.*, 88, 611.
Lapage, C. P. (1932). *Archives of Disease in Childhood*, 7, 235.
Mitchell, A. G. (1930). *Amer. J. Dis. Child.*, 40, 101.
Peter, K. (1927). *Untersuchungen über Bau und Entwicklung der Niere* Heft 2. Jena.
Prader, A. (1950). *Helv. paediat. Acta*, 5, 392.
Woolf, L. I. (1951). *Gt. Ormond Str. J.*, 1, [no. 2], 61.
—— and Giles, H.McC. (1956). *Acta paediat. (Uppsala)*, 45, 489.

ACUTE CEREBELLAR ATAXIA

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Acute cerebellar ataxia occurring in childhood is a definite clear-cut syndrome, yet only three cases appear to have been reported in the British literature (Batten, 1907; Taylor, 1913), although more recently cases with similar features have been included in wider surveys on encephalitis by Brewis (1954) and on ataxia by Shanks (1950). Typically the clinical picture is characterized by the sudden onset of ataxia in a previously well child. The infant staggers, falls and acquires a drunken, uncertain gait; there is often a gross intention tremor, staccato speech and frequently nystagmus. There are no signs of meningeal irritation, fever is absent and the infant remains alert with no alteration of consciousness. Despite these alarming signs the prognosis is generally favourable and recovery takes place over a period of time ranging from a few days to six months.

The object of this paper is to report seven further cases of acute cerebellar ataxia, to discuss those already reported and to draw attention to a syndrome which, if unrecognized, may result in disorders of a more serious nature being diagnosed.

Case Reports

M.B. 239854. A boy of 5 years, who had been progressing normally both physically and mentally, developed an urticarial rash and a low-grade fever. His mother thought he was incubating measles and kept him in bed for three days. He remained rather listless and after a week his temperature rose to 102° F., but this resolved spontaneously without treatment. A week later he became unsteady on his legs and his mother noticed that he seemed unable to keep his eyes still. He was admitted to the Royal Hampshire County Hospital where he was found to be afebrile, but he was lethargic and had ataxia of the trunk and of all four limbs. There was nystagmus and a convergent strabismus, though the ocular fundi were normal; there was generalized hypotonia, and the reflexes were sluggish and the plantar responses were flexor. He had slight neck stiffness and a lumbar puncture showed a clear colourless fluid under normal pressure with 3 leucocytes and a protein content of 80 mg. %.

He was transferred to The Hospital for Sick Children, Great Ormond Street, with the provisional diagnosis of a cerebellar tumour. By this time the nystagmus had disappeared, but he remained apathetic and would only sit up if he were able to hold on to some support. The lower limbs remained ataxic, the deep reflexes were brisk and there was ill-sustained ankle clonus, together with extensor plantar responses.

Investigations included: Haemoglobin 89%, W.B.C. 7,700 per c.mm., with a normal differential, B.S.R. 5 mm. in one hour. A Mantoux test (1:1,000) was negative. Radiographs of the chest and skull were both normal. The C.S.F. on this occasion contained 10 W.B.C. per c.mm., 30 mg. protein per 100 ml. and 67 mg. sugar per 100 ml. A ventriculogram was entirely normal.

Over the next fortnight he continued to improve, the ataxia became less marked and normal muscle tone returned. When examined two months after the onset of the illness he was very well and the only residual sign was a slight intention tremor.

M.H. 254707. A boy was born on December 21, 1953. He was seen at the age of 22 months because of vomiting and a staggering, unsteady gait. He was the second child of healthy unrelated parents; he was born after a normal pregnancy and weighed 7 lb. 3 oz. at birth. He had begun to walk normally when 12 months old and had been steady on his feet until three weeks before admission when he developed a considerable tremor of both arms and legs. When this had been present for 10 days he began to vomit after most meals and lost weight.

On examination he was seen to be a small, wide-eyed little boy weighing only 19 lb. He was afebrile and there was no alteration of consciousness. The skin was rough and he was moderately dehydrated. There was a variable coarse nystagmus, the ocular fundi were paler than normal, but there was no papilloedema. A pronounced intention tremor was present in both arms, there was a tremulous fluttering of the eyelids and a definite rapid tremor involving the head and trunk. He was ataxic and unable to walk, although the power and sensation in his lower limbs appeared normal. There was considerable hypotonia of the trunk and legs, the knee and ankle jerks could not be obtained, but the plantar responses were extensor.

Investigations included radiographs of the skull and chest, both of which were normal. The haemoglobin was 88% (13·02 g. per 100 ml.) and W.B.C. 8,400 per

c.mm. with a normal differential. Lumbar puncture produced a clear fluid under normal pressure which contained no cells; the protein was 30 mg. per 100 ml. but one week later this had risen to 240 mg. per 100 ml. still without any cells. The sugar content was 78 mg. per 100 ml. on both occasions and the Wassermann reaction was negative. The B.S.R. was 2 mm. in one hour and the electrophoretic strip showed a persistently low γ globulin.

He gradually improved over the course of the next month, the nystagmus disappeared, the tremor became less marked and feeding became easier. After a further three weeks he began to walk again, to talk and to feed normally. When last seen, three months from the beginning of symptoms, he was vastly better and could walk unaided.

A.B. 248538. A.B., aged 18 months, was admitted to hospital because of a generalized tremor which had come on with alarming suddenness the day before. He was the first child of Jewish parents and previously had been entirely healthy. His milestones were normal and he had been walking since 1 year. There was no recent history of immunization or of contact with any infectious illness. The day before admission he was more fretful than usual and he held on to the furniture to steady himself when walking. By the afternoon it was noticed that his arm shook when he attempted to suck his finger, and by the evening he was quite unable to stand. There was no vomiting and no alteration of consciousness.

When examined 24 hours after the onset of the illness he had a coarse intention tremor involving the entire body. He was ataxic and had a tremulous cry. There was universal hypotonia of limbs and trunk, although the reflexes remained brisk and symmetrical, and the plantar responses, extensor. Apart from a coarse nystagmus, the cranial nerves were normal. The ocular fundi and the ears showed no abnormality. Although there was some voluntary resistance to neck movement, no true meningism could be demonstrated. The temperature was 98·6 degrees F.

Laboratory investigations included lumbar puncture which gave clear fluid under normal pressure, containing 43 cells per c.mm., mainly mononuclears, 30 mg. protein, 56 mg. % sugar and 720 mg. % chlorides. Leucocytes numbered 7,400 (polymorphs 54%, lymphocytes 46%). A skull radiograph was normal. The Wassermann reaction was negative. The B.S.R. was 5 mm. in one hour. A Mantoux test (1 in 1,000) was negative. The electrophoretic pattern was normal. Complement-fixation tests for toxoplasmosis were negative. An E.E.G. (Dr. Cobb) gave a normal sleep record.

His condition worsened for 48 hours, the tremor became even wilder and he was only happy when lying flat. The reflexes were increasingly brisk and ankle clonus was obtainable for two/three days. He remained extremely ataxic for six weeks and was very difficult to feed, as any effort on his part provoked such gross tremor. Gradually he began to improve, the cells in the C.S.F. fell to 10 per c.mm. with a protein of 80 mg. %.

Three months after the beginning of the illness he developed a squint with a right external rectus weakness and a lumbar encephalogram was carried out to exclude a posterior fossa tumour. It was entirely normal. He has continued to improve slowly, but six months after the onset he is still unable to walk and it appears likely that there is considerable mental impairment.

J.E. 178295. J.E., a girl of 5 years, was admitted on January 7, 1952, because of a sudden onset of tremor and inability to walk. In the past she had received treatment for recurrent attacks of pyelitis and her appendix had been removed. Since that time she had been well until a week before coming to hospital, when she developed an upper respiratory infection with coryza, cough and fever. This was settling, although two days before the onset of neurological symptoms her temperature had been up to 103° F. On the day of admission she became very tremulous and was unable to stand, as any movement provoked a gross intention tremor. She was ataxic and her speech was slurred, she had vomited, but was free from headaches except when she coughed.

Examination revealed a fair-haired girl with a rather immobile facies. She was afebrile, alert and cooperative but frightened to move. There was no neck stiffness and the ocular fundi were normal; there was nystagmus on looking either to the extreme right or left. All limbs were hypotonic yet the reflexes were brisk, the knee jerks pendular and the plantar responses flexor. There was no muscle tenderness, but gross incoordination and intention tremor of the legs and arms. Sensation was normal.

Lumbar puncture produced a clear C.S.F. with 27 cells, mainly lymphocytes, a protein of 30 mg. and sugar 76 mg. %. A blood count gave: Haemoglobin 95%, W.B.C. 8,600 (53% polymorphs, 41% lymphocytes, 6% monocytes).

She became worse for the first 48 hours in hospital, the tremor became more exaggerated, the vomiting continued and an intragastric drip was necessary. In addition she was unable to pass urine and had to be catheterized. By the third day she was beginning to improve, and although she complained that the bed was rotating she was no longer sick. A further lumbar puncture contained 6 cells, with 20 mg. protein and normal sugar and chlorides.

Gradually over a month her speech returned to normal, the ataxia and tremor diminished, although the hypotonia and lack of coordination in the performance of fine movements persisted. Not for a further two months had her gait returned to normal and it was 15 weeks from the onset before she was discharged from convalescence.

J.B. 252728. A boy, born on September 9, 1951, was seen at the age of 4 because nine days previously he had fallen on getting out of bed and had been unsteady on his feet ever since. On the first day of the illness he had had numerous falls and had vomited a number of times. His limbs appeared weak, particularly the left arm, he continued to stagger and remained very miser-

able. His temperature was normal, he had no headache and there was no disturbance of sphincter control.

He was a well-nourished 4-year-old who held his head over to the right, and walked with an unsteady gait. There was hypotonia of all limbs, but the tremor and inability to perform fine movements was most marked in the left arm. There was no meningism, no nystagmus and the ocular fundi were normal. All the tendon reflexes were brisk and the plantar responses were extensor. Investigations were essentially normal. The B.S.R. was 4 mm. in one hour, radiographs of the skull and chest showed no abnormality, the Wassermann reaction was negative, the C.S.F. contained 3 cells per c.mm. with normal protein and sugar content.

During the next week he began to improve, he became much happier, he staggered less and there was no more vomiting. Six weeks after the onset of the illness his gait had returned to normal, the tendon reflexes were no longer brisk and the plantar responses were flexor. He has been seen at intervals over the last two years and he remains entirely well.

J.R. 251293. A girl of 10½ years was admitted to The Hospital for Sick Children, Great Ormond Street, because for the past week she had been unsteady on her feet and had been vomiting. Two months previously she had developed a squint and had suffered from double vision, but this cleared after one week and she had been well until the sudden onset of ataxia and vomiting. She was the third child of healthy parents. At the age of 4 she had had staphylococcal pneumonia, but had otherwise been well. On examination she was found to be rather drowsy, the pupils reacted sluggishly to light, there was a bilateral external rectus weakness and a poorly sustained nystagmus. The ocular fundi were normal. There was slight facial asymmetry, the mouth drooping on the left. The tone was normal, but there was considerable ataxia with dysdiadokokinesia of all four limbs. The reflexes were symmetrical the knee jerks were pendular and the plantar responses flexor.

She continued to be rather drowsy and vomited if she attempted to sit upright. At no time did she complain of headache, there was no fever and no signs of meningism. Laboratory investigations showed: Haemoglobin 88% (13·02 g. per 100 ml.), W.B.C. 8,300 (neutrophils 78%, lymphocytes 22%). The C.S.F. was clear and colourless, it contained 10 white cells per c.mm., 120 mg. per 100 ml. of protein and 69 mg. per 100 ml. sugar. An E.E.G. by Dr. Dickson at the National Hospital, Queen Square, showed marked asymmetry between the two sides suggesting that the left hemisphere was probably involved. In an effort to exclude a posterior fossa tumour a lumbar encephalogram and a ventriculogram were done and were both normal. After one month in hospital she had improved considerably, she was much more alert, there was no vomiting and she was able to walk unsupported on a wide base. Nystagmus was still present, there was a marked intention tremor but the ataxia was much less pronounced.

When seen four months after the onset of the illness she had returned to school and was able to walk a mile there and back each day. On examination a mild residual cerebellar deficit was apparent, but this appears to be improving and causes her no inconvenience.

C.H. P.P. C.H. was a doctor's daughter of 18 months who had been well until a week ago when she began to vomit. The next day she was noticed to be walking unsteadily and by the evening of that day there was a pronounced stagger. She continued to vomit that night and by morning was unable to stand. The temperature remained normal, there was no meningism, no nystagmus and the ocular fundi showed no abnormality. She held her head over to the left and had a left internal strabismus. The tendon reflexes were normal and the plantar responses extensor. After three days she began to improve, and after a further two days she was able to walk with a tottery, wide-based gait. In view of her rapid improvement she was not admitted to hospital and no investigations were carried out. Over the next two weeks she made a complete recovery and there are no residual sequelae.

Reported Cases

Batten writing in 1907 was the first to draw attention to this syndrome in Great Britain. He reported the case of a boy of 11 years who without preceding illnesses suddenly developed a headache and ataxia. He was found to have nystagmus and some loss of tone, together with active knee jerks; there was a rapid improvement so that in three weeks the child was completely recovered. Claude and Schaeffer (1911) published their findings in two cases of ataxia seen in Paris. The second of these, a child of 3½ years, showed the typical picture of acute cerebellar ataxia with recovery after three months. Taylor (1913) described the syndrome in two patients aged 7 and 10 years and he contrasted their sudden onset and benign prognosis with the poorer outlook in two other patients with 'progressive congenital cerebellar ataxia'. The same year Merle (1913) reported the case of a boy of 6 years who recovered after an illness lasting three weeks characterized by a sudden onset, ataxia and tremor, and in which the cerebrospinal fluid contained an excess of protein.

Griffiths in three papers (1916, 1920, 1921) described four additional cases and reviewed the literature up to that time. Of the 31 cases he quotes, all but six had had an acute infectious illness just before the onset of neurological symptoms. They differ from acute cerebellar ataxia in a number of features and fall more readily into the group of post-infective encephalitides. With the exception of six cases (two of Griffiths' own and those of Taylor, 1913; Batten, 1907; and Seham, 1919) there had been a preceding illness such as measles, pertussis, typhoid or varicella which had become worse with

the onset of convulsions or loss of consciousness. This was followed by varying degrees of ataxia, but in addition there were other signs of widespread involvement of the brain, paresis, loss of sphincter control, aphasia and disturbances of sensation were often present. The condition persisted for many months and frequently left residual mental changes. Although in acute cerebellar ataxia there may be evidence that the cerebrum is partially involved, the other signs of brain damage are not seen and this, together with the more favourable prognosis, is sufficient reason for regarding it as a separate entity.

Barbonneix (1928) reported five cases of ataxia occurring in childhood, of which three appear to be typical cases of acute cerebellar ataxia.

In 1944 Klingman and Hodges reported seven cases of acute ataxia of unknown origin occurring during the preceding three years in New York. Six of these appear to be typical examples of acute cerebellar ataxia and one is of particular interest in that although there was complete recovery of function the illness was followed by a conduct disorder of moderate severity. One case (5. F.M.) is unusual in that he had convulsions associated with ataxia, but no other signs of cerebellar dysfunction, and for that reason has not been included in this series.

The single case of Keller and Karelitz (1948) is interesting in that both clinical and E.E.G. findings were suggestive of a diffuse process involving the cerebellum and mid-brain. Both this and the comparatively prolonged illness is very similar to Case A.B.

An excellent account is given by Thieffry, Martin and Arthuis (1953). They describe eight cases seen between 1948 and 1951 in Paris, all of which made a complete recovery. They comment particularly on the pleocytosis sometimes observed in the C.S.F. and on the favourable outcome. A recent paper of Berglund, Mossberg and Rydenstam (1955) from Stockholm reports the findings in five typical cases and is particularly important for the virus studies carried out on them.

It has been possible to extract from the literature a total of 33 cases whose pattern is similar and which appear to be examples of the same syndrome. These, together with seven of our own cases, form the basis for this analysis.

Symptomatology

Onset. The onset in all cases is acute. Often the disease comes on with such devastating suddenness that the parents are able to state the hour at which it began. It attacks previously healthy children usually of the toddler age group and within six to 12 hours they are completely incapacitated. In one case reported by Thieffry *et al.* the onset of ataxia came on with such rapidity during a railway journey from Baden-Baden to Paris that the family assumed that their 3½-year-old son must indeed be drunk. Shanks (1950), in his review of 39 cases of cerebellar ataxia occurring between 1929 and 1949 in Glasgow, pointed out that in general a sudden onset was associated with a good prognosis, whereas those that came on insidiously tend to do badly. Although six out of 17 cases with an acute onset had suffered from other illnesses in the preceding three weeks and must be considered as post-infective encephalitides, a number of his cases are doubtless examples of acute cerebellar ataxia, but unfortunately no case histories are given.

Ataxia. The initial complaint is usually that the infant can no longer walk normally. He either staggers and falls or else refuses to make any attempt to walk. In those who are only moderately affected there is an unsteady, drunken gait with the feet wide apart. In others the ataxia may be so gross that they are only comfortable when lying prone. Case A.B. became immediately distressed if even his head was raised from the pillow. In all cases there was a total inability to adapt to changing postures during voluntary movements. This was frequently the first noticeable symptom and it persisted when other symptoms had cleared.

Tremor. This varied from a mild intention tremor to gross rhythmic movements involving all parts of the body. In particular there was a considerable tremor of the upper limbs, in one case of sufficient magnitude to prevent the infant having his thumb in his mouth. There was a tremor of the head, especially on attempting ocular fixation and when being fed. Perhaps the most constant tremor is that involving the eyes; there was a pronounced tremulous fluttering of the eyelids in three of our cases. This has been noted in numerous other cases, and like the infant reported by Keller and Karelitz (1948), it may persist even during sleep. In addition there may be dissociated tremulous movements of the eyes which become gross when trying to fix on an object.

Nystagmus. This was present in five of our cases, but was only commented on in 13 out of 33 cases in the literature. In our cases any attempt at ocular fixation provoked a coarse oscillatory nystagmus of a cerebellar type. Nystagmus disappears early in the course of recovery and may no longer be obtainable even when a considerable degree of ataxia is still present.

Hypotonia. Hypotonia may be very marked. It was very obvious in four of our seven cases and was a consistent finding in those reported by Thieffry *et al.* It was a notable feature in 12 cases taken from the literature and was present in a further three. In most instances this lack of muscle tone was associated with increased knee and ankle reflexes. These were usually symmetrical and occasionally ankle clonus could be elicited when the disease was at its height (in two of our cases and two in the literature, Goldwyn and Waldman, 1953).

Other Symptoms. Speech was affected in more than half the cases; in the older children a staccato tremulous enunciation developed, whilst in the younger age group they made little attempt to speak, but a tremor was often apparent in the cry. A squint was present in four of our cases and it received comment in eight of those taken from the literature. It was usually due to an external rectus weakness, it often appeared relatively late in the illness, and persisted for only a short time.

It is perhaps equally important to draw attention to the absence of certain symptoms and signs which serve to distinguish acute cerebellar ataxia from similar conditions. Even among the older children headache was an uncommon symptom. It was absent in all our cases and it is only recorded in four cases in the literature, but it is important to realize that over half the cases are below the age of 3 years and are perhaps unlikely to complain of headache. In none of the cases were there signs of meningism. A number of children were disinclined to move their heads because of the vertigo it caused, but none had any demonstrable neck rigidity. Likewise, Kernig's and Lasègue's signs were constantly negative in our cases and in those from the literature in which they were tested.

Again fever was remarkable by its absence. In Case J.E. the child had an upper respiratory infection and a temperature of 103° F. two days before the onset of tremor and ataxia, although it was normal by the time she was admitted to hospital. Only two of 33 cases taken from the literature were febrile; Taylor's (1913) second case ran a fever between 99 and 102° F., but it is perhaps significant that this child had an associated otitis media. Again the case (A.G.) reported by Klingman and Hodges (1944) had tonsillitis and a temperature of 102° F. at the onset of neurological symptoms. It would seem probable that on the occasions when the child has been febrile there have been coincident illnesses to account for it and that it is not part of the symptomatology of acute cerebellar ataxia.

Investigations

Since this survey covers cases reported over a period of 50 years, their mode of investigation naturally varies very widely. In the earlier studies the possibility of syphilis or tubercle being causal agents were excluded by finding negative Wassermann and Mantoux reactions. In the more recently reported cases greater emphasis has been placed on virus studies and on the findings of the electroencephalogram.

Haematology. Data are available in only a few cases. There is no evidence of anaemia. The white blood count is slightly raised, average 10,000 cells per c.mm., but the differential counts showed a normal distribution. The blood sedimentation rate as recorded in seven cases was always within the normal range.

C.S.F. Reports of the composition of the cerebrospinal fluid are available from a total of 30 cases. Characteristically it was a clear, colourless fluid under normal pressure. The white cell content varied between 0 and 90 lymphocytes per c.mm., although in the majority of cases it was normal and only six cases had counts of over 10 cells per c.mm. The protein was usually within normal limits at the initial lumbar puncture, but when subsequent examinations of the C.S.F. were carried out one to four weeks after the onset the number of cells had frequently fallen and the protein content risen considerably. In Case M.H. no cells were present at any time; 10 days after the onset of symptoms the protein was 30 mg. per 100 ml., a week later it had risen to 240 mg. per 100 ml. and after one month it was 140 mg. per 100 ml. Again, J.R.'s initial protein level rose from 40 mg. per 100 ml. to 120 mg. per 100 ml. during the first fortnight of her illness. This change receives little comment in the literature and this is probably due to the disinclination to perform more than a single diagnostic lumbar puncture. It was found in three of our cases and is reminiscent of the pattern found in poliomyelitis. The sugar and chloride contents were always within the normal range whenever they were recorded.

Radiological Studies. Radiographs of the skull were examined in a total of 22 cases and no abnormality was found on any occasion. Ventriculography was carried out in three of our cases and in a further six reported in the literature. The majority were entirely normal. Keller and Karelitz's case showed 'slight cortical atrophy' and Klingman and Hodge's Case 6 was said to show a moderate degree of atrophy.

Electro-encephalogram. This was studied in 14 cases and was normal in eight. Of the others, four showed a slow, 4-5 cycles per second rhythm, especially over the occipital region, and one of these had reverted to normal when re-examined two weeks after the beginning of the illness (Berglund *et al.*). Keller's case was interesting in that the E.E.G. showed a diffuse process with the maximum damage in the mesencephalic region, an observation which was in accord with the clinical findings.

Toxoplasmosis was considered as a possible aetiological agent, but both the dye and complement-fixation tests were negative in three cases in which they were carried out (Cases A.B. and M.M. and Case 5 reported by Berglund *et al.*). The most fruitful investigations have been in the field of virus studies and they are considered in the section on aetiology.

Aetiology

Despite the small number of cases which have been described this syndrome appears to be widespread both in time and space. For the last 50 years sporadic cases have been reported from time to time occurring both in America and throughout Europe. No common aetiological factor has come to light, but the appearance of cases of acute cerebellar ataxia does seem to have been more common during epidemics of influenza, encephalitis lethargica and poliomyelitis. It may occur in children of all ages. The youngest in this series was 15 months and the eldest 11 years. Half the cases were under the age of 3 at the time of onset, and only six out of 40 were over 5. The condition affects primarily the pre-school child and as yet no case of infection by contact has been reported. Likewise previous illness does not appear to play any part in its aetiology nor, unlike the progressive forms of cerebellar ataxia (Friedreich's, Sanger Brown, etc.), can any hereditary linkage be discerned.

Acute cerebellar ataxia begins with a startling suddenness which is suggestive of an infection and this, together with its similarity to poliomyelitis and the post-infective encephalitides, has focused attention on the possibility of its being yet another virus disease. Klingman and Hodges (1944) tested the serum of four of their patients for neutralizing antibodies against the viruses of St. Louis encephalitis and eastern equine encephalomyelitis and in two others they looked for evidence of infection by louping ill, lymphocytic choriomeningitis, western equine encephalomyelitis and herpes simplex—all with negative results.

The work of Berglund *et al.* is interesting. In two of their cases (Nos. 3 and 4) Type I (Brunhilde) poliomyelitis was found. In Case 3 complement fixation was positive for all three types of poliomyelitis, but neutralizing antibodies were obtained against Type I only. Examination of the faeces showed a growth of cytopathogenic agent Type I. When examined six months after the illness the complement-fixation test had become negative. Similar results were obtained in Case 4, and in Cases 1, 2 and 5 the complement-fixation reaction was positive against influenza A and B, although in these cases significant changes of titre could not be demonstrated so that their aetiological role remains unproven. It is of interest that whereas the cases from which poliomyelitis was isolated ran a mild benign course, those in which influenza was implicated ran a more protracted course.

Virus studies were undertaken in three of our cases; in two no virus was isolated, but in the third a cytopathogenic growth was observed but the virus has not as yet been identified.

Diagnosis

First it is essential to exclude the possibility of a posterior fossa tumour. Four of our seven cases were admitted with this as the most likely diagnosis. The history of a child with a neoplasm is generally one of insidious or intermittent progression, with the gradual addition of symptoms over the course of weeks. It must be very unusual for a tumour to announce its presence with the devastating suddenness typical of acute cerebellar ataxia. The suggestion that such an acute onset might be due to haemorrhage into the substance of a tumour is put forward more often by the diagnostically destitute than it is found by the pathologist. Secondly, by the time a tumour causes the gross disturbance of cerebellar function found in acute cerebellar ataxia it is likely to cause some signs of raised intracranial pressure, which may be detected in the ocular fundi or in the radiograph of the skull. Nevertheless on occasion the possible presence of a tumour cannot be ruled out and it is necessary to resort to air studies. The advisability of performing this investigation in the presence of whatever agent is causing acute cerebellar ataxia has been questioned. Recognition of the existence of this syndrome obviated its necessity in three of our cases, but the others in which it was carried out did not seem to be adversely affected by ventriculography.

Poliomyelitis is difficult to differentiate, a fact which is perhaps not surprising as there is some evidence that the virus of poliomyelitis may also be responsible for acute cerebellar ataxia. Even if

this is true, the symptomatology is different, the patient with poliomyelitis has been ill for two or three days before the onset of neurological symptoms, he is usually febrile, complains of headache and has signs of meningism. In a recent case of 'cerebellar' poliomyelitis confirmed by virus studies, the child had a temperature of 102° F. associated with moderate neck rigidity and appeared much more ill than those with acute cerebellar ataxia, although his tremor and unsteadiness were mild in comparison.

Labyrinthine ataxia is more easily distinguished. It is more a loss of static equilibrium, there is rotatory nystagmus and the patient tends to fall to the side of the lesion, the symptoms being made worse by closing the eyes. There may be an associated deafness or discharge from the ear and tests of labyrinthine function will be abnormal.

Acute demyelinating disease of the Schilder type may come into the differential diagnosis. Here symptoms may come on rapidly, but over the course of days rather than hours as in acute cerebellar ataxia. Visual failure together with mental deterioration, convulsions and weakness of all limbs usually serve to distinguish it, the demyelination affecting primarily cerebral cortex rather than cerebellum. Likewise the cerebellar degenerations should cause little confusion, and their slow progressive nature in persons with a family history of nervous disease enables the diagnosis to be clarified.

The question of trauma or of poisoning will usually be excluded by the absence of a history, but it is well to ask direct questions concerning the possible ingestion of heavy metals, insecticides similar to D.D.T. and perhaps of alcohol.

Recently Burgstedt (1955) has reported two cases of ataxia with loss of muscle tone following an overdose of piperazine during a course of treatment for threadworms. In general the diagnosis of acute ataxia is not difficult once its existence as a syndrome is recognized.

Prognosis

The outlook with regard to life was good in all cases. The average duration of the illness was two months, some cases were so slightly affected that recovery was complete within one week, whilst in others signs could be detected as long as eight months after the onset. Unlike the post-infective encephalitides sequelae are comparatively rare. In one of our cases (A.B.) there appears to be considerable mental impairment, and eight months after the beginning of his illness there is marked lack of response to both visual and auditory stimuli. This is unusual and it is perhaps significant that the acute phase was extremely severe and was associated with a high pleocytosis in the cerebrospinal fluid.

Residual signs of incoordination could be detected up to one year after the onset in four cases, but these were usually mild and did not interfere with normal activities in any way. Behaviour problems were a cause of concern in five cases and in one (Klingman and Hodges, G. S.) it was of sufficient severity to require institutional treatment. The other four children showed mild conduct disorders and in particular emotional reactions to momentary separation from their parents. In this last group it is difficult to decide whether the alteration in temperament is due primarily to the illness or to a period in hospital at an age when children are known to react badly to parental separation. Overall in 40 cases, one appears to have suffered serious brain damage and one has developed a moderately severe behaviour disorder. Full recovery has been the rule in the other 38 children, although some have continued to improve for as long as one year after the onset.

Discussion

The term 'acute ataxia' was first used by Leyden in 1891 and cases similar to those reported here have been described as examples of the 'acute ataxia of Leyden'. In fact the two cases described by Leyden were similar only with regard to the sudden onset of ataxia, they had in addition pareses, with disorders of sensation and showed no tendency to recover after periods up to two years. Acute cerebellar ataxia is probably the most convenient name to denote this syndrome since it is purely descriptive and does not imply any particular aetiology. On the other hand, it may be criticized in that it is equally applicable to cases of cerebellar ataxia coming on suddenly in degenerative diseases of the central nervous system and perhaps the best term is that used by the French workers. They call it 'l'ataxie cerebelleuse aigue curable de l'enfant'.

Acute cerebellar ataxia is fortunately not a fatal condition so that its pathology is unknown. By analogy with cases of encephalitis following measles, rubella, etc., it is possible that there is perivenous demyelination affecting primarily the cerebellum. Recently in a survey involving over 1,000 cases of neurological illness following infectious disease, Miller (1956) and his co-workers were struck by the similarity of the changes in the nervous system produced by a wide variety of different infections. Not only were the clinical pictures following measles, varicella and rubella strikingly similar, but from the histopathological point of view they were indistinguishable. Moreover, identical illnesses may

follow non-specific infections, smallpox vaccination or serum sickness. Miller points out that it is probable that there is some common factor in pathogenesis between the specific initiating infection and the non-specific end-result in the nervous system and that such a common factor may be anaphylactic sensitization.

This concept of neuro-allergy receives support from the experimental work of Kabat, Wolf and Bezer (1949), Lumsden (1956) and others. It is known that parenteral injections of sterile brain tissue in a viscous paraffin oil base with heat-killed tubercle bacilli as adjuvants are capable of producing changes in the brain similar to those found in encephalitis. Adjuvants alone or similar systems with tissues other than brain are incapable of provoking this reaction. Lumsden in a recent review concludes that this work has shown that introduction of a definite biochemical system is capable of producing severe disease in the brain which is of an inflammatory type.

It is perhaps a far cry to suggest that acute cerebellar ataxia is due to a variety of agents, possibly viruses, which in the appropriate hypersensitive host are capable of causing an inflammatory lesion centred primarily in the cerebellum. There are, however, a number of facts which tend to favour this hypothesis. First, no single virus has been implicated as the cause of acute cerebellar ataxia, though it occurs more commonly when epidemics of poliomyelitis, influenza, or encephalitis lethargica are prevalent. The Scandinavian workers produced good evidence to suggest that both the poliomyelitis and influenza viruses were involved. In three cases there was a distinct rise in the protein content of the C.S.F. during the course of the illness with little change in the number of cells; in one case it was 240 mg. per 100 ml. This is perhaps suggestive of an exudative phase with capillary damage in the absence of inflammation. Together with the extremely sudden onset characteristic of 'allergic disorders' these facts lend some support to the hypersensitivity theory.

So far no specific treatment appears to have helped these patients. In two of our cases various antibiotics were given to prevent intercurrent infection, but were without effect on the neurological symptoms. Case A.B. had a course of Vitamin B_{12} in high dosage, but this produced no change. The use of cortisone or A.C.T.H. would seem to be worthy of trial in these cases.

Summary

The condition of acute cerebellar ataxia is described. It is characterized by the dramatic suddenness of its onset in a previously well child. There is ataxia, tremor and frequently nystagmus, muscle tone is diminished although the reflexes are usually brisk. The child is afebrile and is free from headache or meningism. Sensation is unaffected.

Seven cases are reported and these, together with 33 taken from the literature, are analysed. It occurs principally in children under 5 years and recovery is usually complete in two or three months. Rarely the syndrome may persist for considerably longer and in two cases there is evidence of permanent brain damage.

The chief cause of diagnostic confusion is a posterior fossa tumour. The rapid onset of symptoms and the lack of signs of raised intracranial pressure favour the diagnosis of acute cerebellar ataxia.

There is some evidence that this syndrome is due to an abnormal reaction of the central nervous system to the viruses of poliomyelitis and influenza. The possible role of cortisone in treatment is discussed.

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References

Babonneix, L. (1928). *Rif. med.*, **44**, 694.
Batten, F. E. (1907). *Trans. clin. Soc., Lond.*, **40**, 276.
Berglund, G., Mossberg, H. O. and Rydenstam, B. (1955). *Acta paediat. (Uppsala)*, **44**, 254.
Brewis, E. G. (1954). *Brit. med. J.*, **1**, 1298.
Burgstedt, H. J. (1955). *Münch. med. Wschr.*, **97**, 531.
Claude, H. and Schaeffer, H. (1911). *Bull. Soc. méd. Hôp. Paris*, 3 ser., **31**, 192.
Goldwyn, A. and Waldman, A. M. (1953). *J. Pediat.*, **42**, 75.
Griffith, J. P. C. (1916). *Amer. J. med. Sci.*, **151**, 24.
—— (1920). *Amer. J. Dis. Child.*, **20**, 82.
—— (1921). *Amer. J. med. Sci.*, **162**, 781.
Kabat, E. A., Wolf, A. and Bezer, A. E. (1949). *J. exp. Med.*, **89**, 395.
Keller, M. J. and Karelitz, S. (1948). *Pediatrics*, **1**, 754.
Klingman, W. O. and Hodges, R. G. (1944). *J. Pediat.*, **24**, 536.
Leyden, E. (1891). *Z. klin. Med.*, **18**, 576.
Lumsden, C. E. (1956). *Proc. roy. Soc. Med.*, **49**, 148.
Merle, P. (1913). *Bull. Soc. méd. Hôp., Paris*, 3 ser., **36**, 325.
Miller, H. (1956). *Proc. roy. Soc. Med.*, **49**, 139.
Seham, M. (1919). *Arch. Pediat.*, **36**, 531.
Shanks, R. A. (1950). *Archives of Disease in Childhood*, **25**, 389.
Taylor, E. S. (1913). *Guy's Hosp. Rep.*, **67**, 98.
Thieffry, S., Martin, C. and Arthuis, M. (1953). *Arch. franç. Pédiat.*, **10**, 14.

WATER DIURESIS IN CHILDREN AGED 1-3 YEARS

BY

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It is now well established that newborn animals and infants are unable to excrete as great a percentage of a test dose of water as adults of the same species (Table 1). The age at which this function of the kidney matures in human beings has been varyingly assessed as 3 months (Ames, 1953) to between 6 and 10 years (Ohlmann, 1920). It therefore seemed of interest to see what percentage of a water load given by mouth is excreted by children aged 1-3 years, especially as this may be of clinical interest in controlling intravenous fluid therapy in this age group.

Moreover the choice of parameter for comparing renal functions in adults and infants is still in doubt. McCance and Widdowson (1952) advocate in theory the use of total body water as a parameter but in practice use body weight. Smith (1951) states that 'there is no *a priori* basis upon which to select any one standard of reference, body weight, surface area, or kidney weight'. However, Smith has some slight preference for kidney weight, and he points out that in man the correlation between kidney weight and surface area is greater than between kidney weight and height or body weight. Other workers (Barnett, Vesterdal, McNamara and Lauson (1952), Calcagno, Rubin and Weintraub (1954) prefer to use body surface as a measure of comparison between renal functions of adults and infants. Barnett *et al.* (1952) state that the failure of others to observe water diuresis in young infants may have been due to 'comparison being made between adults and infants who were given doses of water equivalent on a weight rather than a surface basis'.

In view of these difficulties two parameters (body weight and surface area) were used in the present investigation.

TABLE 1

WATER DIURESIS IN NEWBORN ANIMALS AND IN MAN

Species	Age	Authors	Water Load (ml./100 g. Body Weight)	% Water Load Excreted	Period of Observation (min.)
Rat	1–2 days	Heller (1947, 1951)	4–5	20 (approx.)	145
	7–8 days			30 (approx.)	
	14–16 days			55 (approx.)	
	Adults			85 (approx.)	
	Newborns	McCance and Wilkinson (1947)	5	13·4*	180
	4 days			40·8*	
	12 days			55·0*	
	Adults			39·2*	
Guinea-pig	Newborn	Dicker and Heller (1951)	5	50	180
	Adult			115	
Dog	2 days	Adolph (1943)	5	40 (approx.)	240
	8 days			80 (approx.)	
	25 days			100 (approx.)	
Man	Newborn	Ames (1953)	3	10 (approx.)	180
	3 days			35 (approx.)	
	7 days			50 (approx.)	
	6–18 days	McCance *et al.* (1954)	5	55 (approx.)	240
	Adults			95 (approx.)	
	Newborns to 3 months old	Aschenheim (1919)	200 ml. per child	23–77 (approx.)	240
	Newborns—3 months old	Ohlmann (1920)	200 ml. per child	70 (approx.)	240
	3–6 months old		200 ml. per child	80	

* Recalculated from data.

Methods

The renal response to water was tested by the method of Fishberg (1939). Sixteen children were the main subject of the investigation, none of them had any evidence of renal, hepatic or cardiac disease and they were all at the end of a period of convalescence. They were fasted overnight (12 hours) and on the following morning a catheter was inserted. Eight children were then given 860 ml. water/m.² body surface by stomach tube. A further eight children received 22·0 ml. water/kg. body weight. The total water load of five children included in the latter group contained 25 ml. of deuterium oxide. Virtual deuterium space was calculated from the deuterium concentration of specimens of urine obtained between the second and third hours after the water load had been given. Urine specimens were collected hourly. Deuterium was estimated by a photoneutron method (Haigh, 1954; Haigh and Schnieden, 1956). Nine healthy adults were also tested after a similar overnight fast. These lay down on reaching the laboratory and only got up to pass urine. Following the procedure of McCance, Naylor and Widdowson (1954) they were not catheterized. Urinary osmotic pressure was measured by estimating freezing point depression. The specific gravity of the urine was estimated using an urinometer but when the volume of urine for estimation was small the method of Heller (1940) was used. Four children and one adult were rejected from the series because they vomited following the administration of water.

Results

Tables 2-4 show that the maximum concentrations of urines obtained from the children after

TABLE 2

RENAL RESPONSE TO A WATER LOAD OF 860 ML./M² BODY SURFACE IN ADULTS

Patient No.	Sex	Age (Yr.)	Diagnosis	Total Water Load (ml.)	Water Load (ml./kg.)	% Water Load Excreted in 3 Hours	Maximum Concentration of Urine (Sp.G.)	Minimum Concentration of Urine (Sp.G.)
1	M	22	Healthy adult	1,720	20·2	109	1·023	1·002
2	M	35	,, ,,	1,560	22·5	106	1·024	1·001
3	M	24	,, ,,	1,500	26·0	103	1·024	1·001
4	M	23	,, ,,	1,500	22·0	111	1·024	1·002
5	M	19	,, ,,	1,600	25·6	118	1·012	1·001
6	M	27	,, ,,	1,500	22·0	107	1·020	1·001
7	M	23	,, ,,	1,650	22·1	110	1·023	1·002
8	M	21	,, ,,	1,560	22·8	85	1·025	1·001
9	M	29	,, ,,	1,590	24·2	104	1·017	1·001

TABLE 3

RENAL RESPONSE TO A WATER LOAD OF 860 ML./M² BODY SURFACE IN CHILDREN

Patient No.	Sex	Age (yr.)	Diagnosis: Convalescent from	Total Water Load (ml.)	Load (ml./kg.)	% Water Load Excreted in		Maximum Concentration of Urine		Minimum Concentration of Urine	
						3 Hours	4 Hours	Sp.G	mosM/1	Sp.G.	mosM/1
10	M	2 2/12	Bronchopneumonia	430	32·6	82	84	1·021	813	1·001	65
11	F	2 1/12	Primary T.B.	450	35·5	93	95	1·022	796	1·001	59
12	M	2 2/12	Tonsillitis	430	38·5	81	82	1·002	748	1·002	45
13	M	2 2/12	Cervical gland	437	42·0	77	82	1·025	824	1·002	97
14	F	2 11/12	Bronchopneumonia	500	36·9	89	91	1·023	749	1·002	48
15	M	2	Gastroenteritis	450	38·2	104	105	1·016	792	1·001	86
16	M	2 6/12	Bronchopneumonia	470	36·1	101	104	1·017	623	1·001	54
17	M	1 10/12	Bronchopneumonia	370	31·2	64	69	N.D.	N.D.	1·003	161

TABLE 4

RENAL RESPONSE TO A WATER LOAD OF 22 ML./KG. BODY WEIGHT IN CHILDREN

Patient No.	Sex	Age	Diagnosis: Convalescent from	Total Water Load (ml.)	Water Load (ml./m.)	Water Load Excreted in		Maximum Concentration of Urine		Minimum Concentration of Urine	
						3 Hours	4 Hours	Sp.G.	mosM/1	Sp.G.	mosM/1
18*	F	2 6/12	Otitis media	235	47·0	60	67	1·020	714	1·003	134
19*	M	1 5/12	Upper respiratory infection	210	44·5	113	118	1·019	732	1·001	54
20*	M	2 9/12	Admitted ? petit mal, no evidence found	275	45·5	103	108	1·015	670	1·001	62
21*	F	1 2/12	Pneumonia	220	50·0	73	78	1·024	870	1·001	62
22*	F	2 7/12	Otitis media	255	52·1	85	N.D.	1·017	660	1·001	154
23	M	2 9/12	Anaemia	272	46·5	101	109	1·023	790	1·001	51
24*	M	1 7/12	Pneumonia	215	53·1	88	100	1·021	754	1·003	129
25	M	2 5/12	Bronchitis	268	48·5	54	59	1·024	615	1·003	97

* These children were given deuterium oxide.

withdrawal of food and water for 12 hours does not differ significantly from those in adults (mean ±S.E.: adults, 1·022±0·002; children, 1·021±0·002), t=0·5, P>0·5).

The minimum concentration of urine obtained in the adults varied between a specific gravity of 1·001 and 1·002 whilst the minimum concentration in children varied between 1·001 and 1·003.

Fig. 1 shows that infants aged 1½-3 years who

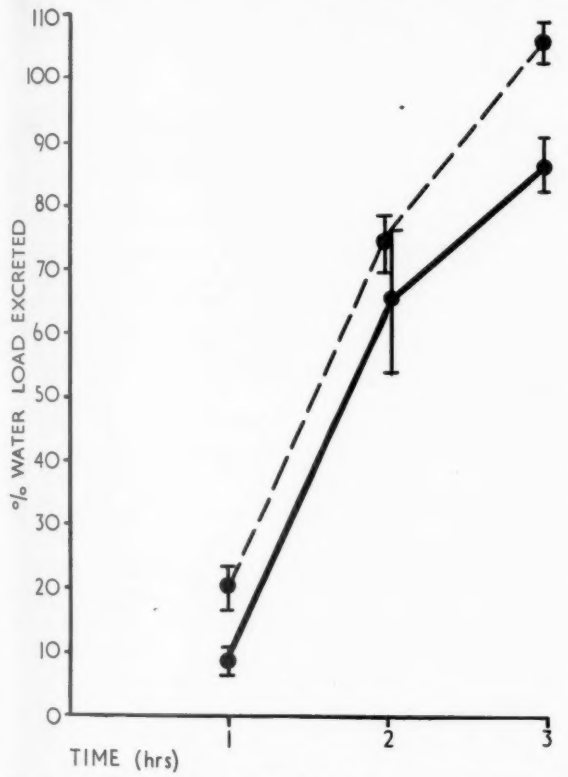

FIG. 1.—The renal response (mean±S.E.) to water of a group of eight children between the ages of 1½ and 3 years.
● - - - ● adults. ● ——— ● children.

were given a water load of 860 ml./m² did not in three hours excrete as much of their water load as adults (mean±S.E.: adults, 105·9±3·0; children, 86·4±4·6, t=3·63, P>0·001). The difference remains significant (children, 89·5±4·0; adults, 105·9±3·0, t=3·3, P>0·001), even if infant 17, who was under 2 years old, is excluded. In fact Tables 2-4 show that the percentage of the water load excreted by the children in four hours did not quite attain that excreted by the adults in three hours.

Children of the same age group who were given a water load of 22 ml./kg. excreted in three hours 84·6±5·8% of their water load only and in four hours 91·3±8·7% as compared with the excretion of 105·9±3·0 by adults in three hours. The difference is again significant at three hours (t=3·2, P>0·001).

The mean virtual deuterium space in five infants was 62·6±1·7% of the total body weight (Table 5). These results are in good agreement with those of Friis-Hansen, Holiday, Stapleton and Wallace (1951) who found that in five children aged 1 year 3 months to 3 years 10 months, deuterium space varied between 58·2 and 62·8% of their body weight.

Discussion

The results obtained indicated that in children up to the age of 3 years the capacity for water diuresis lay between that of newborn infants and adults although it clearly approached that of adults rather than of infants. This conclusion applied whether the water load was given in relation to surface area or to the body weight of the child.

McCance *et al.* (1954) advocated the use of total body water as a parameter. Assuming, as they did, that a 70 kg. man has 42 litres of body water (equals 60% of the body weight), a water load of 1,500 ml. (which equals a load of 22·0 ml./kg. body weight or 860 ml./m² if the surface area of such a person is taken as 1·73 m²) represents a water load per litre of body water of 35·5 ml. In the present series the water load per litre of body water given to infants 18-24 varied from 32·5 to 38·5 ml. (mean±S.E., 35·2±1·1). This suggests that the water load per litre body water was much the same in the experiments on adults (Table 2) as in the children of group 18-25, although there was a significant difference in water diuresis.

The results of this investigation are more in keeping with those of Ohlmann (1920) than those of Ames (1953). The former found that five children aged between 1 and 4 years excreted an average of

TABLE 5
VIRTUAL DEUTERIUM SPACE (TOTAL BODY WATER) IN FIVE CHILDREN

Patient No.	Virtual Deuterium Space (% body weight)	Total Water Load (ml.)	Water Load/Litre Body Water
18	56·9	235	38·5
19	64·8	210	34·0
20	61·2	275	36·0
21	62·1	220	35·1
24	67·9	215	32·5

68% of their water load. However, the procedure employed by Ohlmann (1920) differed appreciably from that of Ames (1953): Ohlmann gave 400 ml./child whilst Ames gave 30 ml./kg. body weight.

Other tests of kidney function suggest that renal maturation is not complete for several years after birth. Smith (1951) states that the inulin clearance, the renal plasma flow and the maximal rate of tubular p-aminohippuric acid excretion do not attain adult levels until the child is at least 2 years old.

It may be argued that the children investigated were not healthy. Whilst it is not denied that they all had been recently ill, they had all recovered and were fit for discharge on the day after the test. It is unlikely therefore that the difference of approximately 20% found between the urinary excretion of water by the children and adults is due to their previous illness. But since, as Heeley and Talbot (1955) have shown, the insensible water loss per day is considerably higher in infants than in adults, it may have been due to that difference.

Summary

The renal response to water of 16 children between the ages of 1½ and 3 years was tested. Eight children received a water load of 860 ml./m^2 body surface, the others a water load of 22·0 ml./kg. body weight. The children concentrated their urine as well as adults but, in contrast to adults, did not excrete a volume of urine equal to that of the test dose within three hours. The virtual deuterium oxide space in five children was determined. The question of parameters for the study of kidney functions is discussed.

I would like to thank Professor A. V. Neale and Dr. J. Apley of the Bristol Royal Hospital for Sick Children for permission to investigate their patients and also the medical students who kindly participated in the investigation. I am grateful to Professor H. Heller for his criticisms and to Dr. C. P. Haigh for the estimations of deuterium.

References

Adolph, E. F. (1943). *Physiological Regulations*, Lancaster, Pa.
Ames, R. G. (1953). *Pediatrics*, **12**, 272.
Aschenheim, E. (1919). *Z. Kinderheilk.* (*Orig.*), **24**, 281.
Barnett, H. L., Vesterdal, J., McNamara, H. and Lauson, H. D. (1952). *Amer. J. Dis. Child.*, **84**, 481.
Calcagno, P. L., Rubin, M. I. and Weintraub, D. H. (1954). *J. clin. Invest.*, **33**, 91.
Dicker, S. E. and Heller, H. (1951). *J. Physiol.* (*Lond.*), **112**, 149.
Fishberg, A. M. (1939). *Hypertension and Nephritis*, 4th ed. Philadelphia.
Friis-Hansen, B. J., Holiday, M., Stapleton, T. and Wallace, W. M. (1951). *Pediatrics*, **7**, 321.
Haigh, C. P. (1954). Radioisotope Conference, 1954, p. 101. London.
—— and Schnieden, H. (1956). *J. Physiol.* (*Lond.*), **131**, 377.
Heeley, A. M. and Talbot, N. B. (1955). *Amer. J. Dis. Child.*, **90**, 251.
Heller, H. (1940). *J. Physiol.* (*Lond.*), **98**, 3P.
—— (1947). *Ibid.*, **106**, 245.
—— (1951). *Archives of Disease in Childhood*, **26**, 195.
McCance, R. A. and Wilkinson, E. (1947). *J. Physiol.* (*Lond.*), **106**, 256.
—— and Widdowson, E. M. (1952). *Lancet*, **2**, 860.
——, Naylor, N. J. B. and Widdowson, E. M. (1954). *Archives of Disease in Childhood*, **29**, 104.
Ohlmann, J. (1920). *Z. Kinderheilk.* (*Orig.*), **26**, 291.
Smith, H. W. (1951). *The Kidney*. New York.

CONGENITAL DIABETES MELLITUS AND NEONATAL PSEUDODIABETES MELLITUS

BY

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Diabetes mellitus is very rare in infants. Cases in recent years have been reported by Schwartzman, Crusius and Beirne (1947), by Bertoye and Stefani (1954) and by Keidan (1955), who reviewed the hitherto published cases of infantile diabetes. In Keidan's report 79 cases of infantile diabetes are mentioned, the neonatal cases attracting special interest on account of certain clinical characteristics.

These cases have also been published under such varying headings as congenital diabetes (Ambard, Merklen, Schmid, Wolf and Arnovljevitch, 1925; Feldmann, 1928; Nevinny and Schretter, 1930; Schretter and Nevinny, 1930; Wylie, 1953) and neonatal diabetes mellitus (Lewis and Eisenberg, 1935). Several of the congenital cases have been but insufficiently investigated, and Lawrence and McCance (1931) by an exact clinical analysis could reject a number of these as being unproved congenital cases. In most cases falling in this group (Kitselle, 1852; Morrison, 1916; Ambard *et al.*, 1925; Feldmann, 1928; Schretter and Nevinny, 1930; Nevinny and Schretter, 1930) the diabetic mother as well as the child died at parturition.

Of proved cases of congenital diabetes there is the case reported by Guest (1949) in which diabetes was diagnosed on the ninth day after parturition, and Wylie's (1953) case discovered at the age of 2 weeks. Both of these cases resulted in permanent diabetes. The remaining cases of neonatal diabetes may be divided into two groups, the first of which may be called neonatal diabetes mellitus and into which can be put cases reported by Cuno (1910), Kochmann (1922) (these two cases are, however, doubtful) Lewis and Eisenberg (1935), Limper and Miller (1935), Devine (1938), Gans (1954), Hofman-Bang (1954) and Hickish (1956). Most of these cases of diabetes have had an abrupt course with a fatal outcome. The other group comprises diseases which differ not only from the other cases of neonatal diabetes, but also from all other instances of diabetes, because they all had a good prognosis and all were cured (Ramsey, 1926; Lawrence and McCance, 1931; Strandquist, 1932; Nawrocka-Kanska, 1952; Arey, 1953; Keidan, 1955; and Nelson, 1954). The majority simultaneously showed a marked infectious state which, however, was not considered of primary aetiological importance. The abnormal carbohydrate metabolism has generally lasted two or three weeks only and as a rule has yielded to insulin therapy. In a few cases a cerebrally conditioned diabetic state has been suspected (Nawrocka-Kańska, 1952; Keidan, 1955). They have been described under various designations, for example, 'temporary diabetes' (Lawrence and McCance, 1931), 'transient diabetes' (Arey, 1953; Keidan, 1955). Strandquist (1932) speaks of 'infantile glycosuria simulating diabetes' and Nelson (1954) of 'diabetes mellitus syndrome in the newborn infant'. As a common name for this condition we suggest 'neonatal pseudodiabetes mellitus'.

Case Reports

Case 1. A boy was born on February 3, 1953, at the Obstetric Department in Lund. The parents were healthy, without any diabetic heredity. The pregnancy had a normal course, but the patient was delivered by means of low forceps on account of threatening foetal hypoxia. His birth weight was 2,780 g. (6 lb. 2 oz.) and length at birth 49 cm. (19 in.). The child showed pronounced signs of postmaturity (Fig. 1) and was referred to stage III

FIG. 1.

in Clifford's (1954) classification of placental dysfunction.

The patient's weight fell to 2,300 g. (5 lb.) and he became cachectic, although alert. He began to vomit and on the fifth day after parturition was transferred to the Pediatric Department in Lund suspected of an endocrine-metabolic disorder. Glycosuria was proved, non-protein nitrogen was 35 mg./100 ml. and the blood sugar was as high as 720 mg./100 ml. In the course of the following days the blood sugar was about 400 to 500 mg./100 ml., the glycosuria was maximally 13% but there was no ketonuria.

At first the patient was fed on small quantities of breast milk, with plenty of fluid and electrolytes. Testosterone was also administered. On this therapy the weight was maintained unchanged, the blood sugar was about 500 mg./100 ml. but the patient showed no ketosis and the general condition was surprisingly good. More breast milk was now allowed and the blood sugar was further increased to about 600 mg./100 ml. and at the same time Legal's test became positive.

At 3 weeks of age insulin therapy was instituted.

Initial laboratory tests showed eosinopenia, as well as signs of hypokalaemia. Cholesterol and phospholipids were pathologically increased, 254 and 454 mg./100 ml. respectively. The sugar in the cerebrospinal fluid was 380 mg./100 ml. Insulin, starting with 4 i.u. NPH-insulin was given, the dose being gradually increased to 8 i.u. which was soon reduced again to 6 and finally to 4 i.u. On the second day the patient was ketone-free and the blood sugar values fell to between 250 and 300 mg./100 ml. After three weeks we changed over to the same dosage of 4 i.u. IZS (Lente) and after the lapse of a little less than a week the patient showed no sugar in the urine and the blood sugar was normal.

Two weeks later we experimentally omitted the insulin for four days. Immediately there was glycosuria, and the blood sugar rose abruptly to 350 to 400 mg./100 ml. and for this reason we again began to administer insulin in the same dosage, 4 i.u., first NPH and later, after two weeks, IZS (Lente). Some days after the change-over to IZS (Lente) the blood sugar was again normal and the urine free of sugar. The insulin was continued for another three weeks and then was discontinued for good. At that time the patient had been treated with insulin for a total of three months.

The patient was kept in hospital for three further weeks and all the time he appeared normal as regards the blood and urinary sugars. The day before he was discharged there was a mean blood sugar level of 130 mg./100 ml. and a delta blood sugar (= Δ B.S.), *i.e.*, the difference between the maximum and the minimum values of the blood sugar curve, of 70 mg./100 ml. At discharge the patient had increased his weight by 3·5 kg. and thus more than doubled his birth weight by the age of 4 months (Fig. 2).

Since his discharge in June, 1953, the patient has been examined several times. The blood sugar has been normal, there has been no glycosuria, and repeated glucose tolerance tests have proved normal too, most recently three years after discharge.

FIG. 2.

Case 2. A girl was born on April 1, 1955, at the Obstetric Department of the Centrallasarett in Vänersborg. The parents were healthy, without any diabetic heredity. The mother was healthy during pregnancy. Confinement was normal and at term. The patient measured 47 cm. but weighed only 2,020 g., was strikingly thin, greyish-pale and sucked poorly. The weight dropped to 1,860 g. on the third day of life and then began to increase slowly.

On the eleventh day of life glycosuria and a urinary specific gravity as high as 1·029 was ascertained. A blood sugar test showed 400 mg./100 ml. and during the following three days the blood sugar rose to 440, 480 and 560 mg./100 ml. An isolated test for urinary sugar at the age of 14 days showed 7·8%. No ketonuria was found. The patient was fed with breast milk in the usual quantities but fed poorly during the first two weeks.

At the age of 14 days insulin therapy was begun with 6 i.u. IZS (Lente). In response to this the glycosuria disappeared, the specific gravity of the urine fell to about 1·005, and the blood sugar began to fall. At the age of 19 days the insulin dosage was increased to 8 units. Afterwards the patient did well except on one occasion when she showed an insulin reaction due to an alteration in the diet owing to a misunderstanding. The patient's weight increased quickly and at the age of 3 months she weighed 3,970 g.

Gradually the blood sugar tended to fall and simultaneously it became more stable, and the insulin dosage was reduced to 6 i.u. at the age of 37 days, to 4 units on the 57th day and finally was discontinued on the 200th day. The patient was kept at the hospital for another fortnight, and during this period the blood sugar was stable at a level of 90 to 160 mg./100 ml. A glucose tolerance test on the eighth day after discontinuing the insulin with 1 g. glucose per kg. body weight showed an increase of the blood sugar to 190 mg./100 ml. after 75 minutes and a return to the level of 100 mg./100 ml. within three hours. A later test at the age of 1 year showed normal blood sugar levels and no urinary sugar. The child's length was 76 cm. and weight 10,160 g.; somatic and mental development were quite normal.

Discussion

It is open to discussion whether one is justified in calling these cases diabetic. Lawrence and McCance (1931) considered the diagnosis of diabetes mellitus justified if the patient showed diabetic symptoms and a glycosuria exceeding 2% or a clear recurrent hyperglycaemia above 200 mg./100 ml. Most of the above mentioned cases directly comply with these criteria, although Keidan's (1955) cases, for example, never showed pronounced hyperglycaemia. The fact that the diabetic condition was cured in these cases challenges *a priori* the diagnosis of diabetes mellitus. Joslin, Root, White and Marble (1952) have warned against exaggerated optimism, and claim a five-year period without recurrence as a criterion for recovery. In diabetes in children one might be justified in claiming curability even if the cases in question cannot claim a five-year period without recurrence. The three-year observation period of Case 1 of this report should be sufficient for regarding this case as recovered.

The absence of ketosis in these cases, at any rate, is remarkable, especially considering that the hyperglycaemia was often excessive. This may be explained partly by the type of diabetes in question here, and partly because a newborn infant seldom reacts with ketosis. As a general rule these cases of temporary diabetes have had but little need for insulin, and Keidan (1955) indeed asks whether insulin therapy really is necessary. In this connexion it may be said and emphasized that an attempt to discontinue it in our first case immediately resulted in aggravated conditions of the blood and urinary sugars. However, it is correct when Keidan (1955) points out that any greater insulin sensitivity is not always present initially. Because of these departures from the usual clinical picture of diabetes we would suggest the use of the term neonatal pseudo-diabetes mellitus.

An analysis of previously reported cases gives reason to suspect some of the patients to be postmature. Ramsey's (1926) case weighed 2,200 g. (about 5 lb.), Strandquist's (1932) and Arey's (1953) cases too weighed 2,200 g. each, and Keidan's (1955) patient 2,790 g. (6 lb. 2 oz.) though born at term. One of our cases weighed 2,780 g. and was clearly postmature, the other weighed 2,020 g. (about 4½ lb.) though born at term. It cannot be ignored that there has been postmaturity in a number of the cases described in the literature similar to our Case 1 where there were pronounced signs of postmaturity, *i.e.*, a placental dysfunction or insufficiency.

Arey (1953) has postulated that in his case it was a question of a hyperadrenocorticism, and Keidan (1955) suggests a hypothalamic effect in his case. Much can be said in favour of the assumption that in these patients with neonatal pseudo-diabetes mellitus we are dealing with a carbohydrate disturbance of a steroid-diabetic character. In favour of this hypothesis is the occurrence of hyperglycaemia without ketosis, the relatively weak insulin sensitivity and curability. If in these cases, as at least in one of ours, a placental dysfunction led to postmaturity in the infant it is reasonable to presume a carbohydrate of a steroid-diabetic nature. It is known that the hormonal activity in the placenta even includes secretion of corticosteroids of the '11-oxy' type. Priscilla White (1956) has thought that in these cases it is a stress or steroid type of condition.

Whether the alpha-cell dominance in the islets of the pancreas prevailing in an infant of this age—with the consequent hyperglucagonaemia—has any bearing on the occurrence of neonatal pseudo-diabetes mellitus cannot be decided. A discussion of this problem may even be of a theoretical nature only. The exact mechanism of these pseudo-diabetic cases thus so far is obscure and continual investigations are of the greatest value. If the urine is systematically examined in all infants during the neonatal period more cases would no doubt be recognized.

At present it cannot be said whether an actual diabetes mellitus will develop in these patients later on. However, it seems unlikely and the case reported by Ramsey (1926) at a follow-up examination 25 years later was normal. However, it may be advisable to make control tests in connexion with infections or other conditions that might act as a releasing factor for a latent diabetic disposition.

Summary

The authors report two cases of temporary diabetes during the neonatal period. Previously reported cases of the same nature are analysed and the term 'neonatal pseudo-diabetes mellitus' for this condition is suggested.

References

Ambard, L., Merklen, P., Schmid, Wolf and Arnovljevitch (1925). *Bull. Soc. méd. Hôp. Paris*, **49**, 547.
Arey, S. L. (1953). *Pediatrics*, **11**, 140.
Bertoye, P. and Stefani, A. (1954). *Pédiatrie*. **9**, 147.
Clifford, S. H. (1954). *J. Pediat.*, **44**, 1.
Cuno, F. (1910). *Jb. Kinderheilk.*, **71**, 623.
Devine, J. (1938). *Archives of Disease in Childhood* **13**, 189.
Feldmann, I. (1928). *Zbl. allg Path. path. Anat.*, **42**, 435.
Gans, B. (1954). *Proc. roy. Soc. Med.*, **47**, 132.
Guest, G. M. (1949). *Acta paediat. (Uppsala)*, **38**, 196.
Hickish, G. (1956). *Brit. med. J.*, **1**, 95.
Hofman-Bang, E. (1954). *Acta paediat. (Uppsala)*, **43**, 393.
Joslin, E. P., Root, H. F., White, P. and Marble, A. (1952). *The Treatment of Diabetes Mellitus*, 9th ed. Philadelphia.
Keidan, S. E. (1955). *Archives of Disease in Childhood*, **30**, 291.
Kitselle, J. F. (1852). *Kinderheilanstalt*, **18**, 313.
Kochmann, R. (1922). *Jb. Kinderheilk.*, **99**, 20.

Lawrence, R. D. and McCance, R. A. (1931). *Archives of Disease in Childhood*, **6**, 343.
Lewis, E. and Eisenberg, H. (1935). *Amer. J. Dis. Child.*, **49**, 408.
Limper, M. A. and Miller, A. J. (1935). *Ibid.*, **50**, 1216.
Morrison, H. (1916). *Boston med. surg. J.*, **175**, 54.
Nawrocka-Kańska, B. (1952). *Pediat. pol.*, **27**, 1067.
Nelson, W. (1954). *Textbook of Pediatrics*, 6th ed., p. 1286. Philadelphia.
Nevinny, H. and Schretter, G. (1930). *Arch. Gynäk.*, **140**, 39[illegible].
Ramsey, W. R. (1926). *Trans. Amer. pediat. Soc.*, **38**, 100.
Schretter, G. and Nevinny, H. (1930). *Arch. Gynak.*, **143**, 4[illegible].
Schwartzman, J., Crusius, M. E. and Beirne, D. P (1947). *Amer. J. Dis. Child.*, **74**, 587.
Strandquist, B. (1932). *Acta paediat.* (*Uppsala*), **13**, 421.
White, P. (1956). Personal communication.
Wylie, M. E. S. (1953). *Archives of Disease in Childhood*, 28, 297.

DIABETES MELLITUS IN A 2-MONTH-OLD CHINESE BABY

BY

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Diabetes mellitus in infancy has been reported time and again since the first case was described in 1789, and Schwartzman, Crusius and Beirne (1947) collected all the cases so far reported in the literature and added one of their own. Since then Brodribb, McMurry and Scott (1952) described two further cases and in 1953 Wylie reported a case of congenital diabetes diagnosed in a child aged 17 days. In all the above cases the symptoms which brought the child to hospital had varied from failure to gain weight, polydipsia and polyuria to symptoms as a result of infection, and subsequent investigations had revealed glycosuria and hyperglycaemia. The case to be described presented with a rather unique complaint offered by the mother, namely, an observation that ants were attracted to the wet napkin of the child, although Kitselle (1852) quoted by Schwartzmann *et al.* (1947) noted honeyed napkins.

Case Report

S.B.L., a 2-month-old female Chinese infant was referred on September 19, 1955, with a history that the mother had noticed for the previous two weeks that ants used to crowd around the wet napkins; also that the child used to cry excessively before her next feed and was pacified by offering her milk or water. The mother did not notice any change in micturition habits. The patient is the eleventh child in the family, born at full term with a normal delivery and a birth weight of 6 lb. The parents and all the other children are alive and well and are free from glycosuria.

On examination, the child was small and weighed 7 lb. 12 oz. The skin was loose and dry, and further clinical examination did not reveal any other abnormality.

The urine showed orange to red reduction to Benedict's solution with a trace of acetone but no evidence of diacetic acid. An osazone test revealed glucosazone crystals. The fasting blood sugar was 280 mg. % and a glucose tolerance test showed values of 350 mg. % at half an hour, 540 mg. % at one hour, 560 mg. % at one and a half hours and 535 mg. % at two hours—a definite diabetic curve. The urine during the test showed orange to red reduction of Benedict's solution with a positive test for acetone in all samples. The microscopical examination of the urine did not reveal any abnormality, and the Mantoux tuberculin test was negative to 1 in 1,000 and 1 in 100.

The diagnosis of diabetes mellitus in an infant was made and treatment started. From published reports, it was noted that infant diabetics were very sensitive to insulin and it was decided to start the child on 1 unit of soluble insulin before a feed and slowly work up the dose, checking on the blood sugar. On this schedule it was noted that 2 units of soluble insulin before a feed brought the blood sugar down to approximately 120 mg. % and urine green to Benedict's with no acetone two hours after a feed. When this was achieved, 7 units of insulin zinc suspension (IZS-lente) were given just before the first feed once a day, and the urine tested before each feed. It was found that the first and last specimens usually showed light orange while the other specimens were blue to green. Acetone was absent in all specimens. The child was observed on this schedule for some time and she progressed well. She was fed three hourly, six feeds a day, consisting of reconstituted full-cream dried milk with added dextrimaltose, and the approximate number of calories ingested daily from this milk mixture was 425.

On October 2, the child had a fit, became drowsy and the hands and feet twitched. The skin was cold and clammy and knee and ankle jerks were increased with bilateral Babinski signs. The pupils were dilated but fundi were normal. A clinical diagnosis of hypoglycaemia was made, the blood for sugar estimation was taken and an intravenous drip of 5% dextrose in 0·2% sodium chloride was given. The blood sugar was found to be 75 mg. % and urine was blue to Benedict's reagent. The child was finally brought out of the coma after two days and soluble insulin substituted before each feed depending on the urine reaction, and the IZS was finally adjusted to 4 units daily and the child did not give any more trouble. A subsequent glucose tolerance test still showed a diabetic curve.

The child was discharged on December 12, 1955, after the parents had been taught how to inject the IZS each morning and she is still being followed up in the Outpatient Department.

Comments

The above is probably a case of true pancreatic diabetes and not of transient hyperglycaemia as a

result of infections or intracranial pathology since the child still shows a diabetic glucose tolerance curve. It has been shown again, as in the above case, that the response of infant diabetics to insulin is capricious, and, in the light of experience of previous writers, the child was started on very small doses of insulin and worked up. Even then, the child had an attack of hypoglycaemic coma when it was thought that she was sufficiently stabilized. She was placed on a régime of IZS because it was considered that frequent injections of soluble insulin would overtax the parents too much and chances of infection would be increased. Apparently, the child responded well to this régime.

Wylie, in her report, noted that diabetes diagnosed under the age of 6 months, after excluding the two cases described by Ramsey (1926) and Lawrence and McCance (1931), where there were only a transient hyperglycaemia with glycosuria, had hitherto claimed a 100% mortality. Her case survived and is still presumably alive. The child described above is still alive at the time of writing, putting on weight, but the ultimate prognosis is doubtful since her home conditions are really not very satisfactory for giving insulin injections. However, she is being followed up very closely.

Summary

A case is reported of diabetes mellitus diagnosed at the age of 2 months, and is the first case of infantile diabetes in a Chinese to be reported.

The unusual complaint of attraction of ants by the wet napkin is mentioned.

The method of using IZS in treatment is described.

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References

Brodribb, H. S., McMurry, J. and Scott, L. G. (1952). *Brit. med. J.*, **1**, 1060.

Lawrence, R. D. and McCance, R. A. (1931). *Archives of Disease in Childhood*, **6**, 343.

Ramsey, W. R. (1926). *Trans. Amer. pediat. Soc.*, **38**, 100.

Schwartzman, J., Crusius, M. E. and Beirne, D. P. (1947). *Amer. J. Dis. Child.*, **74**, 587.

Wylie, M. E. S. (1953). *Archives of Disease in Childhood*, **28**, 297.

DIFFUSE PROGRESSIVE INTERSTITIAL FIBROSIS OF THE LUNGS IN CHILDHOOD

BY

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Hamman and Rich reported three cases of diffuse fibrosis of the lungs in 1935, and when they met a fourth case after a lapse of nine years (1944) they described in detail this condition under the title 'Acute Diffuse Fibrosis of the Lungs'. Since then it has been referred to as the 'Hamman-Rich syndrome'. The authors stated that the clinical picture—progressive dyspnoea and increasing evidence of myocardial insufficiency—was new to the physician and the anatomical picture new to the pathologist. They considered the disorder as a definite clinico-pathological entity of unknown origin. Clough (1954) and Bradley (1956) collected from the literature 25 similar cases in addition to 20 doubtful or incompletely investigated patients. Some had a subchronic and others a chronic course, the shortest duration being 31 days, the longest nine years. The name 'diffuse progressive interstitial fibrosis of the lungs', which was proposed by Beams and Harmos (1949), appears therefore more appropriate than that originally suggested. The age of the reported patients varied between 21 and 68 years, except for the girl recently reported by Bradley (1956) who was 9 years old at the time of her death. In the British literature, Heppleston (1951) reported one adult case and Sloper and Williams (1955) described another example in an adult. It seems, therefore, that the condition is not well known in this country, and that so far it has not been recognized in early childhood. The case which we now report is that of a boy, 2½ years of age, who presented in a quite unusual clinical picture, features described as characteristic of the Hamman-Rich syndrome, namely a chronic illness with progressive dyspnoea, tachypnoea, cyanosis, increasing evidence of pulmonary hypertension and the development of right ventricular failure.

Case History

A boy, born on February 20, 1953, was under the care of one of us (F.B.) from July 5, 1955, until his death on March 18, 1956 (eight and a half months). He was the third child in a family of three, who lived with their parents and grandparents in overcrowded conditions in a poor area. Most of the members of the household had 'coughs'. His birth weight was 6 lb. 6 oz. He grew in length but had always been thin; he learned to walk and talk at the normal age. At the age of 7 months he had whooping-cough and from that time had attacks of 'bronchitis' at intervals of four to six weeks, each attack lasting about four days. Between attacks he was not free from cough. Because of a more severe attack, he was admitted to hospital on July 5, 1955.

He was an intelligent but very apprehensive child and detailed examination was at first difficult. The general nutrition was poor (weight 26½ lb.) but he was of normal length for his age. The skeletal muscles were poorly developed and hypotonic; the head seemed relatively large and he had prominent though not exophthalmic eyes; the radial epiphyses were enlarged but there was no radiological evidence of rickets; the thorax was flat and the lower costal margins were indrawn; the respiratory rate was 35/min., pulse rate 110-140/min. and the temperature normal. There were remarkably few abnormal signs in the lungs but he had a dry, 'brassy' cough. The heart sounds at this time were closed and of normal intensity. Because of his excitability he was given phenobarbitone and with this his respiration rate fell to between 20 and 30/min. but the pulse rate remained high. Radiological examination showed a diffuse mottling of the lungs with a denser shadow on the right side, medially (Fig. 1).

For two weeks there was little change in his general condition but on July 18 he suddenly became very ill, the respiratory rate rising to 60/min., and he became cyanosed; when he coughed or cried this became intense and the superficial veins became distended; the temperature rose to 99° F. The distress was as great as is seen in acute asthma but the picture as a whole was not that of asthma. Presuming a secondary infection, he was given aureomycin (300 mg. daily for one week). Oxygen was not tolerated. On the third day the respiratory rate fell to 30/min. and the temperature to 98° on the fifth day. By the end of a week, his general condition was better than it had been since his admission and he went home on August 12. He was seen in the Out-patient

FIG. 1.—Radiograph of the chest.

Department on September 12 when he was fairly well, and had gained a little weight. He was reported to have had one short, severe attack of dyspnoea but it passed so quickly that a doctor was not called. He was seen again on October 12 and was then readmitted. He had lost weight, was less well in general and the respiratory rate was 50/min. A few moist sounds were heard scattered over both lungs; the heart sounds were closed but it was now noted that the pulmonary second sound was markedly accentuated. His general condition had not changed much and he was brighter and more friendly. Apart from the tachypnoea he seemed to feel quite well and he sat up and took interest in his surroundings. The respiratory rate was constantly about 60/min. and did not vary during sleep. The pulse rate varied a great deal, even during sleep, from 90 to 150/min. The temperature rose to 99° F. occasionally and on November 15 to 103°. Then he had more severe dyspnoea and the respiratory rate was 60-80 per minute. On aureomycin the temperature fell to normal but the respiratory rate remained high. When he coughed or cried an almost constant cyanosis became much worse and there was a general distension of the superficial veins. There was now some finger clubbing.

He was usually quiet and contented, willing to talk and usually ready to smile. Sometimes he cried out as if in pain. He preferred to sit up, and usually leaned forwards a little in a squatting position. He made no attempt to stand up in his cot and he expressed no desire to be taken out of his cot. His progress varied a little, sometimes he seemed to feel better, but he had attacks of severe dyspnoea from which he recovered in a surprising manner; there was a steady gradual general deterioration.

The physical signs in the lungs were remarkably few, but at times fine crepitations could be heard over small areas. His cough became paroxysmal. After a short course of cortisone which produced a very temporary improvement, the temperature reached a higher level and remained above normal.

In the end of February he developed various small 'haemangiomata' in the skin of the trunk and limbs and, on the anterior abdominal wall, small ulcers. Early in March, signs of right heart failure became gross; oedema, enlargement of the liver and signs of oedema of the lungs. With 'digoxin' and 'mersalyl', there was slight improvement. He died quite suddenly on March 18.

Laboratory Investigations. Repeated radiological examinations showed little change. The first electrocardiogram, taken on November 23, 1955, showed a mild degree of right ventricular dominance, though this was little more than might be expected at this age. However, by February, 1956, the degree of dominance had increased, suggesting that right ventricular strain was greater and that this was secondary to the pulmonary changes.

The haemoglobin level varied between 87 and 100% (Haldane). The total white cell count was usually between 6,000 and 9,000; the highest on one occasion was 17,000 per c.mm. That coincided with a rise in temperature and was probably related to superadded infection. At no time was there an eosinophilia. Pancreatic function was normal and fat absorption was 94·4%. The sweat salt content was normal. Mantoux and Wassermann tests were negative.

Treatment. Treatment was quite ineffective in the control of the disease although antibiotics had some influence on what was thought to be superadded infection. Oxygen was not tolerated. Cortisone produced temporary improvement in well-being but probably hastened the downward trend of the illness.

Clinical Diagnosis. The whole clinical picture was one not previously observed and a tentative diagnosis of the 'Hamman Rich syndrome' was made by exclusion of the more familial post-whooping cough bronchiectasis, pulmonary fibrosis associated with pancreatic fibrosis, chronic lung disease associated with tuberculosis or syphilis, primary congenital heart disease and idiopathic pulmonary haemosiderosis. The exact diagnosis depends on histology and is discussed in detail later.

Post-mortem Findings. Necropsy was performed 29 hours after death. Apart from small ulcers of the skin which were covered by blackish-red crusts and a mild clubbing of fingers and toes, the pathological findings were limited to the lungs and the heart. These were as follows:

There were extensive greenish-yellow membranes of fibrino-purulent exudate loosely adherent to the pulmonary pleura of the left lung and a smaller amount of similar exudate was also present on the right side, mainly in the interlobar space between the middle and lower lobes. The lungs were uniformly firm in consistency. On the cut surfaces a greyish-white network and greyish-red spots were seen, uniformly distributed throughout all lobes of both lungs. Only the upper lobe of the right lung showed a more uniformly consolidated area, dove-grey in colour not unlike the appearance of carnification.

FIG. 2.—Broadening of the interstitial tissue of the lung. Van Gieson plus Weigert's elastic tissue stain. ×120.

When examined with the help of a lens the lungs had the appearance of solid pinkish-grey and greyish-white tissue with numerous holes as if pierced with the tip of a needle. The tracheo-bronchial, paratracheal and other mediastinal lymph nodes were all enlarged, greyish-red and soft. None of them showed any circumscribed lesions, nor any evidence of caseation or calcification. The epicardium of the right auricle was dull in appearance and showed grey and greyish-red spots. The heart was moderately enlarged and the enlargement was due to an eccentric hypertrophy of the right ventricle. The valves, septa and great vessels were normal.

Histological Findings. The submesothelial connective tissue of the lungs is oedematous, shows many distended capillaries and a loose infiltration with polymorphonuclear leucocytes and lymphocytes. The most conspicuous finding is the broadening of the interstitial tissue (Fig. 2). This is most marked in the interalveolar septa and decreases in a proximal direction, being minimal around the larger bronchioles and bronchi. The broadening is due to a variable cellular infiltration and/or fibrosis. Some interalveolar septa are very cellular, show numerous large mononuclear cells and lymphocytes with a few plasma cells and an occasional polymorphonuclear leucocyte (Fig. 3). Capillaries of the septa are often dilated but apparently not increased in number. Fibroblasts are scanty in the cellular areas of interstitial tissue but more numerous in other parts and in such areas a fair number of van Gieson-positive fibres is seen (Fig. 4). In all interalveolar septa an abundance of argentaffine fibres is demonstrable (Fig. 5). Mast cells and eosinophilic leucocytes are absent. The fibrosis is particularly marked in subpleural areas. The alveoli are lined by cuboid epithelium (Figs. 2 and 3). They are compressed, usually circular, but in areas of more advanced fibrosis they form often narrow, occasionally slit-like, tortuous tubules, not unlike those seen in bronchiectatic lungs (Fig. 6). Alveoli, alveolar ducts, bronchioli and bronchi are either empty or they contain groups of large mononuclear cells with a frequently foamy cytoplasm and a few lymphocytes. In some air spaces an acellular pale eosinophilic oedema fluid is seen. Alveolar ducts are sometimes, and respiratory and terminal bronchioles

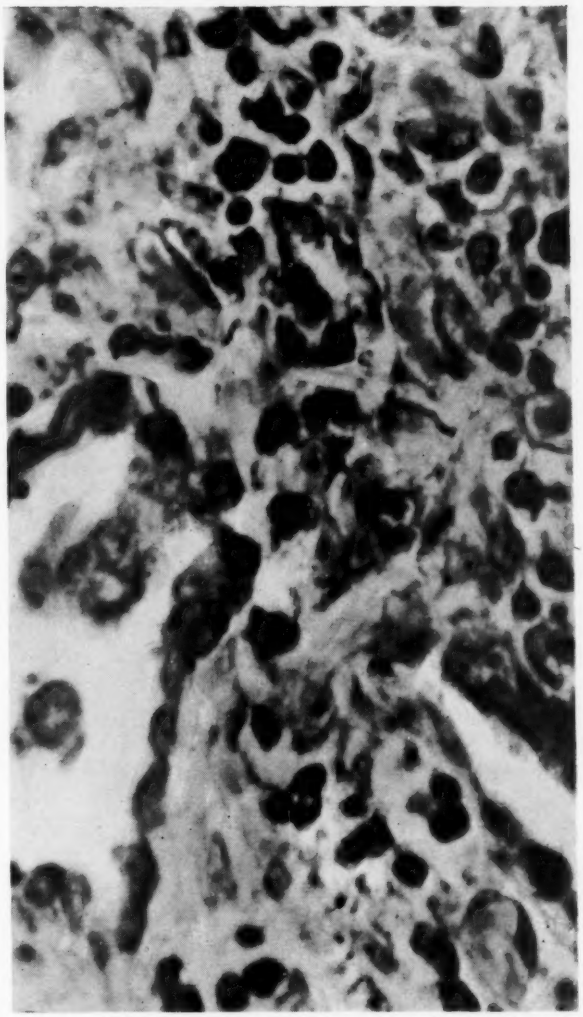

FIG. 3.—Intra-alveolar septum showing large mononuclear cells and lymphocytes with a few plasma cells and an occasional polymorphonuclear leucocyte. Giemsa. ×625.

FIG. 4.

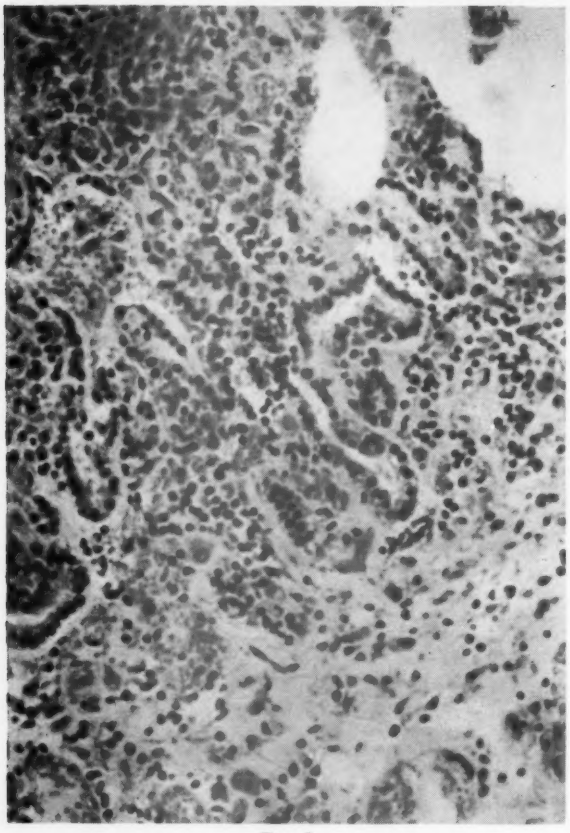

FIG. 6.

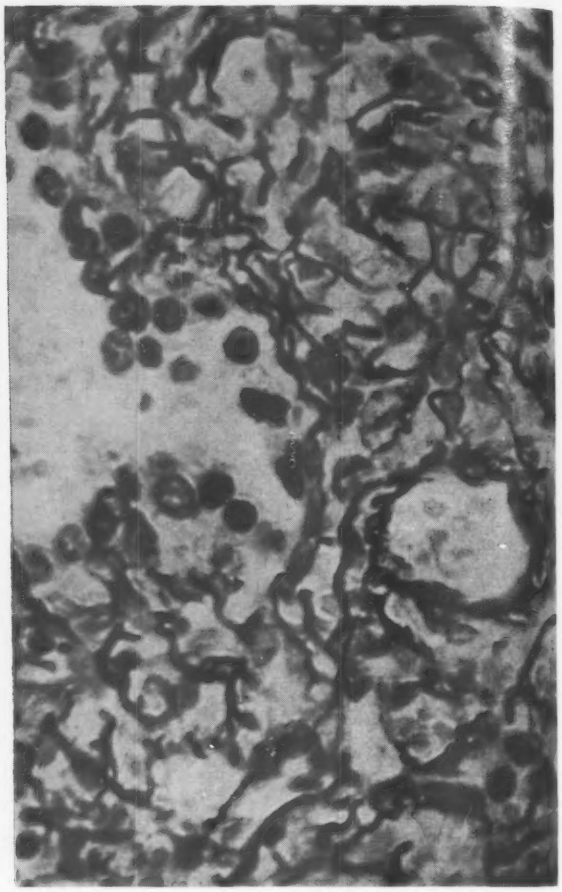

FIG. 5.

FIG. 4.—Interstitial areas of lung stained with Van Gieson plus Weigert's elastic tissue stain. ×192.

FIG. 5.—Interalveolar septum of lung showing argentaffine fibres. Laidlaw. ×625.

FIG. 6.—Alveoli formed into narrow tubules similar to those found in bronchiectasis. Haematoxylin and eosin. ×120.

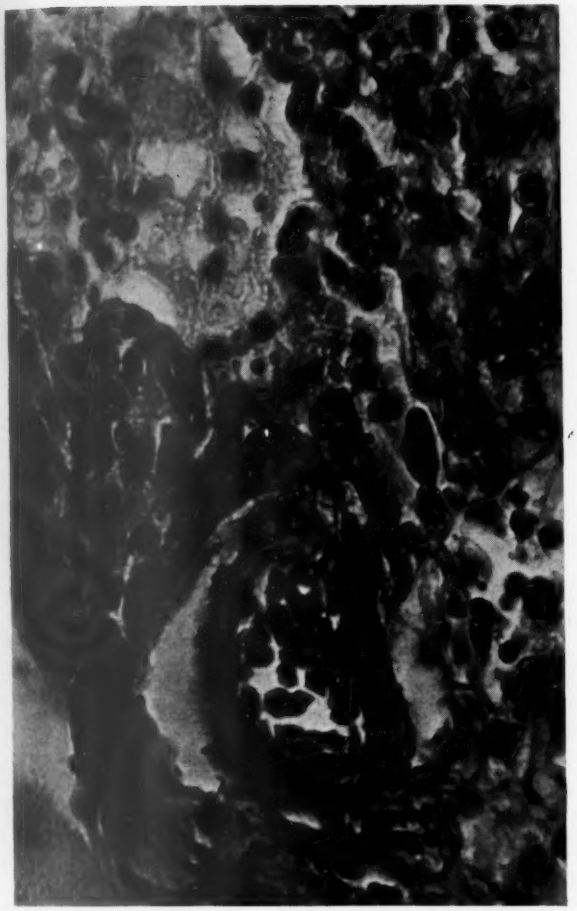

FIG. 7.—Pulmonary arterioles showing muscular media. Van Gieson plus elastic tissue stain. ×466.

often, distended. A few terminal air spaces are partly lined by a hyaline membrane. This is deeply eosinophilic, engulfs sometimes flat cells or is covered towards the lumen by a continuous layer of extremely flattened cells. Fibrin is nowhere demonstrable by Weigert's fibrin-stain or by phosphotungstic acid-haematoxylin, but by acid picro-Mallory deeply red fibres are seen in the interstitial tissue, none within the air spaces. Nowhere is organization of alveolar exudate or a continuity between the alveolar contents and the tissue of the interalveolar septa demonstrable, and cellular infiltration or fibrosis of interalveolar septa shows no relationship to the presence or absence of cells or of eosinophilic material in the air spaces. The bronchi and bronchioli show no ulceration and there is no lymphoid hyperplasia, such as commonly seen in bronchiectasis. Frozen sections stained with Sudan-black showed sudanophil material in many cells of the interalveolar septa and also within the air spaces. With scarlet-red (Herxheimer) considerably less lipids were demonstrable and these were mainly present within the air spaces. No sudanophil material was demonstrable in paraffin sections. Okatomo's reaction for phospholipids (Ueda, 1952) and that with copper-phthalocyanine (Pearse, 1955) were both negative but the Smith-Dietrich method stained a few alveolar macrophages black. With Nile-blue sulphate on frozen sections some of the cells in the air spaces stained dark blue but none red. With the benzidine reaction haemoglobin was demonstrable only in the red cells of the blood vessels. Haemosiderin was present in small amounts in groups of mononuclear cells within the air spaces and only occasionally in interalveolar septa. Treated with P.A.S. the ground substance of the interstitial tissue stained pale pink and a strong reaction was present only in some of the foamy macrophages. This reaction was blocked by acetylation and reversible by KOH treatment. Acid mucopolysaccharides were demonstrable by Rinehart's modification of the Hale method only in a few epithelial cells lining bronchi and bronchioli. None were demonstrable with mucicarmine. With coupled tetrazonium the pale eosinophilic material in some of the air spaces stained pale reddish-brown. Only in a very few places Gram-positive cocci were demonstrable. Pulmonary arterioles of less than 100μ diameter showed a distinct muscular media (Fig. 7) and those of 200μ external diameter had a wall of 50μ in thickness (Fig. 8) (external to internal diameters 2:1 instead of normal 1·2-1·4:1). Elastic fibres in the interalveolar septa were even for this age scanty and a few were fragmented. The elastic membranes of pulmonary arteries were normal.

A bacteriological examination, which included cultures on Sabouraud's medium, gave the following results:

FIG. 8.—Pulmonary arteriole of 200μ diameter showing muscular wall of 50μ diameter. Van Gieson plus elastic tissue stain. ×625.

(1) Pleura, sterile; (2) lungs, a very mixed growth with viridans streptococci, *Proteus*, haemolytic streptococci and *E. coli*, mostly type 086; (3) tonsil, many *Proteus*, *Staphylococcus aureus* and a few *E. coli*, half of which were 086; (4) spleen, a few haemolytic streptococci, *E. coli* and viridans streptococci. After 48 hours a few moniliae were grown from lungs, tonsil and spleen, but none from the pleura. The haemolytic streptococci were not of the Lancefield group A. Virus investigations on the lungs obtained at necropsy were all negative.

The skin of the abdomen was deeply ulcerated with necrotic squamous epithelium, altered blood and pyogenic granulation tissue on the floor but little haemosiderin; the heart showed hypertrophy of muscle fibres of the right ventricle; mediastinal lymph nodes, sinus catarrh; the liver, vacuolation of cytoplasm of the liver cells and congestion with centrilobular haemorrhagic necroses, and the kidneys a few hyaline casts in the collecting tubules.

Discussion

The clinical course of the disease and the histopathological findings fulfil all the criteria described by Hamman and Rich. Reviewing the literature and our own case we would summarize the characteristic findings as follows: The onset is sometimes acute but more often insidious and preceded by a productive or non-productive cough of some duration. Fever is in the beginning usually absent and the main symptom is increasing respiratory distress followed by cyanosis. Clubbing of fingers and toes was present in the majority of cases. The physical findings over the lungs are strikingly scarce, they may be absent or scattered rales may be heard but dullness is absent. In most cases there develops an enlargement of the heart associated with an accentuation of P_2. According to Peabody, Peabody, Hayes and Hayes (1950) the more acute the case the greater the tendency for cor pulmonale to develop. A radiological examination reveals a diffuse mottling or a striking reticulation of both lung fields, not unlike that seen in pneumoconiosis. The symptoms increase progressively and all the reported cases have died after a duration of a few weeks to several years except for the identical twin-sister of a fatal case described by Peabody *et al.* (1950)—who showed suggestive clinical symptoms but was still alive at the time of publication. Pathologically there is a diffuse involvement of all lobes of both lungs although there are differences in the age of the lesion in various areas. Younger and older lesions are irregularly distributed throughout both lungs, except possibly that subpleural lesions appear older. Changes differing in age merge into each other and are never sharply demarcated. Everywhere there is a broadening of the interstitial tissue which is more severe in the interalveolar septa than in the peribronchiolar and peribronchial areas, apparently decreasing in a centripetal direction. The broadening in the younger lesions is due to infiltration with large mononuclear cells, lymphocytes and plasma cells. In older lesions there is a fibroblastic proliferation. Argentaffine fibres are everywhere in the interstitial tissue abundant and collagenous fibres are frequently present in the interalveolar septa. A lymphocytic peribronchial infiltration is inconstant and not conspicuous, and follicle formation rare. The alveoli are lined by a cuboid modified epithelium; they are either empty or contain alveolar macrophages. Fibrin and organized intra-alveolar exudate may be absent or scanty and there is no relationship between the interstitial fibrosis and the presence or degree of organization of intra-alveolar exudate. Inflammatory changes in the bronchi and bronchioli, including ulceration and mural cellular infiltration, may be absent and are never a conspicuous feature. Hyaline membranes, mainly in the terminal bronchioles, were present in almost all cases. Their absence is mentioned occasionally. Here and there bronchioles may be dilated without destructive changes in the walls. These may be interpreted as minute traction bronchiectases. Vascular changes characteristic of pulmonary hypertension were repeatedly described. In our case they consisted of the development of a muscular media in arterioles less than 100μ in diameter. This change was recently studied by Heath and Whitaker (1956) in mitral stenosis (Heath and Whitaker, 1955a), patent ductus arteriosus (Heath and Whitaker, 1955b), Eisenmenger's complex (Brown, Heath and Whitaker, 1955), septal defect (Heath, Brown and Whitaker, 1956a) and idiopathic pulmonary hypertension (Heath, Brown and Whitaker, 1956b). According to these authors 'the earliest signs of pulmonary hypertension in the pulmonary vasculature is the appearance of a muscular media in pulmonary arterioles which normally show no distinct media in human lung'. In addition there was in our case a definite muscular hypertrophy of somewhat larger pulmonary arteries. Proliferation of the subendothelial connective tissue of the intima was absent but is occasionally mentioned in the literature.

The reports in the literature correspond principally to this description and vary mainly in inflammatory changes in bronchioles and the presence of organized exudate in the alveoli which may form 'Masson-like bodies'. An exception is the 35-year-old man reported by Callahan, Sutherland, Fulton and Kline (1952). Here the photomicrographs show in addition to interstitial fibrosis the air spaces filled with honeycombed material like that seen in

pneumocystis pneumonia. It is possible that this is a rare example of pneumocystis infection in an adult; on the other hand the infant described by Donohue (1956) as interstitial plasmacellular pneumonia, where the author stressed the absence of the characteristic pneumocystis masses, may be an example of early progressive interstitial fibrosis of the lungs in childhood, although the author does not mention the presence of fibroblasts or collagenous fibres in the broadened interalveolar septa.

It appears to us that as long as the aetiology of the disorder is unknown, progressive interstitial fibrosis of lungs should be separated from chronic organizing pneumonia. Usually the latter condition is lobar or lobular and not diffuse, affecting uniformly both lungs. Exceptionally, however, the clinical syndrome may be undistinguishable from that described by Hamman and Rich and the post-mortem examination may reveal a uniform affection of both lungs. However, most alveoli are filled with an organized exudate which frequently is connected by a pedicle with the fibrotic interalveolar septum (Fig. 9). We had the opportunity of seeing two such cases (both in adults), one studied by Dr. Kurrein (1956), the other by Professors Arnott and Orr (1956). It is possible that Case 1 of Schechter (1953) is also an example of a chronic diffuse pneumonia with organization of intra-alveolar exudate.

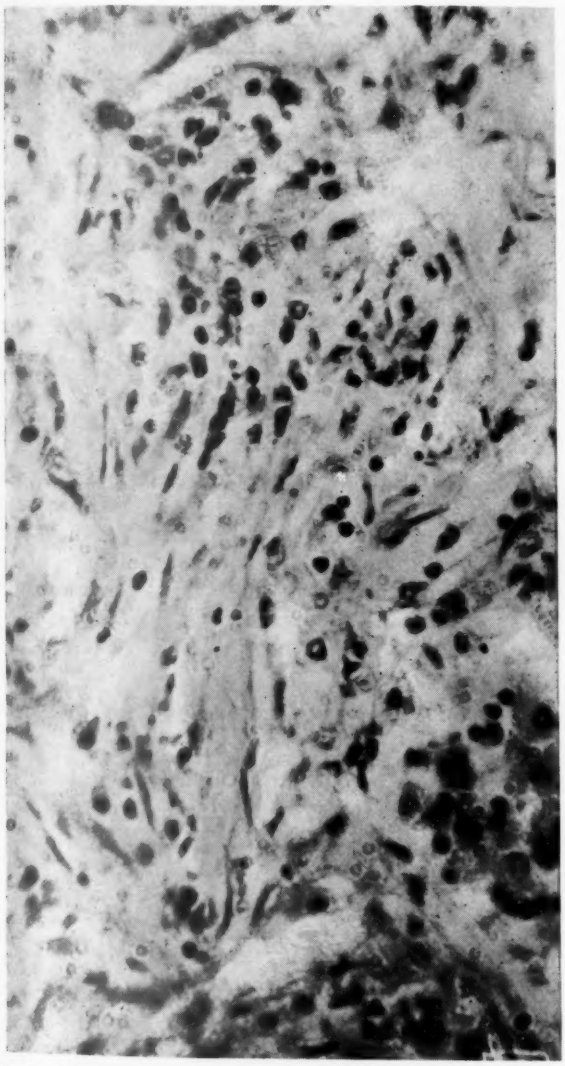

FIG. 9.—Diffuse organizing pneumonia (Dr. Kurrein's case). Haematoxylin and eosin. ×192.

The differentiation of progressive interstitial fibrosis of the lungs from the majority of pulmonary diseases in childhood will rarely present difficulties. Bronchiectasis will be readily diagnosed with the help of *x*-ray examination and bronchography. It is lobar or segmental, the bronchi are dilated or collapsed, filled with purulent exudate and surrounded by conspicuous yellowish-white rings of peribronchial infiltration. There is extensive atelectasis, areas of fibrosis replacing destroyed lung parenchyma and lymphoid hyperplasia with formation of follicles with large germinal centres. The bronchi show ulceration and mural infiltration.

Pulmonary haemosiderosis can be easily differentiated by the presence of anaemia, frequently with splenic enlargement, haemoptysis, and, in the post-mortem examination, by the brown induration of lungs, masses of macrophages laden with haemosiderin and fragmentation of elastic fibres. Pneumocystis pneumonia is usually a disease of young infants aged 2-6 months. It mainly affects premature infants. The demonstration of the parasite in histological sections and particularly in imprints is decisive. Nowhere in progressive interstitial fibrosis of the lungs are such masses of P.A.S.-positive material seen as in pneumocystis pneumonia. Monocytic interstitial pneumonia is a common disease of young infants, particularly in congenital heart disease, and is often diagnosed only by histological examination. Syphilitic pneumonia alba, which affects exclusively newborn infants, will be easily diagnosed by the presence of other syphilitic manifestations and the demonstration of *Treponema pallidum*. 'Atypical pneumonia' is a comparatively benign disease, and does not show the progression characteristic of the 'Hamman-Rich syndrome' or the development of cor pulmonale and finger clubbing. The histological changes were studied on a large amount of material by Golden (1944). The most characteristic lesion consisted of frank pus, desquamated cells of the mucous membranes,

cellular debris and mucoid fluid in the bronchiolar lumina. The bronchiolar walls were constantly ulcerated. The interstitial changes were centrifugal from peribronchiolar tissue into the interalveolar septa. The atypical bronchopneumonia studied by Kneeland and Smetana (1940) showed in the early stages haemorrhagic exudate in the alveoli with normal septa and a tendency to organization of this exudate. The interstitial bronchopneumonia described by Cole and McCallum (1918) complicates fatal cases of influenza, measles and whooping cough. It has been likened by McCordock and Muckenfuss (1933) to the pulmonary changes in rabbits which were intrapulmonally injected with vaccinia virus. In human material of fatal whooping cough the changes consist mainly of mural bronchitis, peribronchitis and peribronchiolitis as described by Feyrter (1927) with less constant and marked involvement of interalveolar septa. In measles there are in addition epithelial giant cells (not pathognomonic). In this disease and some cases of atypical pneumonia acidophilic inclusion bodies may be found. The changes in fibrocystic dystrophy of the pancreas (which is clinically easily differentiated) differ from those in fatal whooping cough only by the greater tendency to the formation of peribronchial abscesses.

A rare disease which may simulate progressive interstitial fibrosis of the lungs is carcinoma of the thymus with retrograde lymphogenous spread into the lungs (Baar, 1954). A radiological examination will often, but not always, reveal the thymic tumour. The morbid anatomical diagnosis will present no difficulty. Lungs may be involved in reticulosis of the Letterer-Siwe type, in sarcoidosis and also in Hodgkin's disease, but manifestations from organs other than the lungs will rarely present clinical diagnostic difficulties and the histological appearance of each of these diseases is entirely different from that of progressive interstitial fibrosis of the lungs.

Changes very similar to those of progressive interstitial fibrosis of the lungs are seen in 'rheumatic pneumonia' and pulmonary manifestations of rheumatoid arthritis (Ellman and Ball, 1948). Rheumatic pneumonia is in most instances not a specific disease but a bronchopneumonia which develops in atelectatic lungs, mainly in the lower lobe of the left lung, in the presence of cardiac failure. Masson bodies may represent organized intra-alveolar exudate but in some instances they develop in the interalveolar septa and are associated with fibrinoid necrosis of connective tissue and accompanied by interalveolar fibrosis. According to Gouley (1938) and to Neubuerger, Grieves and Rutledge (1944) the rheumatic pneumonia develops in three stages: (1) fibrinoid necrosis of collagen in the interalveolar septa, (2) infiltration with round cells, plasma cells and giant cells, (3) fibroblastic proliferation and fibrosis.

Great difficulties may be encountered in the clinical differential diagnosis between progressive interstitial fibrosis of the lungs on one hand and cardiac disease or 'idiopathic pulmonary hypertension' on the other. Silverman and Talbot (1953) made the definite diagnosis *in vivo* with the help of a lung biopsy.

The aetiology of the disorder is at the present time a matter of speculation. Most writers favour a virus aetiology (Spain, 1950) but a non-inflammatory disease related to collagen diseases has also been suggested. Golden and Bronk (1953) consider a 'progressive diffuse alveolar hypertrophy of reticuloangiotic type' as characteristic. No vascular proliferation was present in our case. It appears by no means certain that there is always the same cause. Different causes are suggested by the case reported by Callahan *et al.* (1952), where, in addition to interstitial fibrosis, there were intra-alveolar masses suggestive of *Pneumocystis carinii*. Proliferative changes in the interalveolar septa are in this condition often reported in the continental European literature. It is therefore possible that the progressive interstitial fibrosis of the lungs is a clinico-pathological but not an aetiological entity.

Summary

The second example of progressive interstitial fibrosis of the lungs in a child and the first in early childhood is described. The differential diagnosis, the morbid anatomical and histopathological differences between progressive interstitial fibrosis of the lungs and clinically and/or histologically similar disorders and finally the possible aetiology are discussed.

We wish to thank Dr. K. B. Rogers for the haematological and bacteriological investigations, Dr. Clifford Parsons for the electrocardiographic examination, Dr. R. Astley for the *x*-ray reports, Mr. A. R. Detheridge for technical help and Mr. J. G. Williamson for the photographs.

References

Arnott, W. M. and Orr, J. (1956). Personal communication.
Baar, H. S. (1954). *Öst. Z. Kinderheilk.*, **10**, 2.
Beams, A. J. and Harmos, O. (1949). *Amer. J. Med.*, 7, 425.
Bradley, C. A. (1956). *J. Pediat.*, **48**, 442.
Brown, J. W., Heath, D. and Whitaker, W. (1955). *Brit. Heart J.*, **17**, 273.
Callahan, W. P. Jr., Sutherland, J. C., Fulton, J. K. and Kline, J. R. (1952). *Arch. intern. Med.*, **90**, 468.
Clough, P. W. (1954). *Ann. intern. Med.*, **40**, 641 (Editorial).
Cole, R. and McCallum, W. G. (1918). *J. Amer. med. Ass.*, 70, 1153.
Donohue, W. L. (1956). *Lab. Invest.*, **5**, 97.
Ellman, P. and Ball, R. E. (1948). *Brit. med. J.*, **2**, 816.

Feyrter, F. (1927). *Frankfurt. Z. Path.*, **35**, 213.
Golden, A. (1944). *Arch. Path.* (*Chicago*), **38**, 187.
—— and Bronk, T. T. (1953). *Arch. intern. Med.*, **92**, 606.
Gouley, B. A. (1938). *Amer. J. med. Sci.*, **196**, 1.
Hamman, L. and Rich, A. R. (1944). *Bull. Johns Hopk. Hosp.*, **74**, 177.
Heath, D., Brown, J. W. and Whitaker, W. (1956a). *Brit. Heart J.* **18**, 1.
——, ——, —— (1957). *Ibid.* **19**, 83.
—— and Whitaker, W. (1955a). *J. Path. Bact.*, **70**, 291.
——, —— (1955b). *Ibid.*, **70**, 285.
——, —— (1956). *Circulation*, **14**, 323.
Heppleston, A. G. (1951). *Thorax*, **6**, 426.
Kneeland, Y. Jr. and Smetana, H. F. (1940). *Bull. Johns Hopk. Hosp.*, 67, 229.
Kurrein, F. (1956). Personal communication.
McCordock, H. A. and Muckenfuss, R. S. (1933). *Amer. J. Path.*, **9**, 221.
Neubuerger, K. T., Geever, E. F. and Rutledge, E. K. (1944). *Arch. Path.* (*Chicago*), **37**, 1.
Peabody, J. W., Peabody, J. W. Jr., Hayes, E. W. and Hayes, E. W. Jr. (1950). *Dis. Chest.*, **18**, 330.
Pearse, A. G. E. (1955). *J. Path. Bact.*, **70**, 554.
Schechter, M. M. (1953). *Amer. Rev. Tuberc.*, **68**, 603.
Silverman, J. J. and Talbot, T. J. (1953). *Ann. intern. Med.*, **38**, 1326.
Sloper, J. C. and Williams, E. (1955). *Lancet*, **2**, 533.
Spain, D. M. (1950). *Ann. intern. Med.*, **33**, 1150.
Ueda, M. (1952). *Hyogo J. med. Sci.*, **1**, 117.

APPENDICITIS AND ENTEROBIASIS IN CHILDREN

A HISTOLOGICAL STUDY OF 691 APPENDICES

BY

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When the mucous membranes of the gastro-intestinal organs are fixed by a formol-vapour method the surface of these structures appears to be covered by a 'cellular layer' (considered by orthodox histologists to be formed by a debris of cells, mucus and food remnants). This upper structure can be followed from the corneal layer of the stratified tissue of the oesophageal cardia to its ending in the similar layer of the anal skin. It does not stain by any of the mucin stains, it leaves ash after micro-incineration, it contains a large sequence of nuclei and in some places gives the impression that it contains capillaries (Duran-Jorda, 1946). It was to study its morphological changes in appendicitis that a systematic study was made of appendices removed in this hospital during a period of 21 months, in all a total of 691 appendicular organs.

During this histological study *Enterobius vermicularis* was so frequently found in the sections that it was decided to pay it special attention with the purpose of establishing the role, if any, of the parasite in the aetiology of appendicitis.

Method

The appendix, after removal, was carefully opened and pinned on to the corked lid of a small jar containing undiluted formalin to a depth of 2 cm., and in order to avoid splashing the specimen during transportation to the laboratory, filter paper of the diameter of the jar was left floating in the formalin. After the specimen had been exposed to the fixative for three or four days the jar was opened and the appendix, still attached to the lid, was left for two to three hours in contact with the atmosphere for the surface to dry. It was then cut lengthways, trimmed and immersed in formol-saline. The usual technique of paraffin embedding was then followed, sectioning at 5μ and staining with haematoxylin and eosin.

* Dr. Duran-Jorda died on March 30, 1957.

Microscopic Findings

When the appendicular lumen containing a large number of parasites is studied under the dissecting microscope (Fig. 1) it can be seen that most of the *Enterobius vermicularis* appear covered with some material, but others, especially the young forms, can be seen buried in the organ itself. Microscopically, the appendices fixed by formol-vapour show a layer of cells of varying thickness, forming the uppermost layer of the mucous membrane, monocellular in normal areas and multicellular in acute appendicitis. It is within this layer that *Enterobius vermicularis* is generally found, either singly or with other worms forming groups of three or four side by side (Fig. 2), or resting not only on the mucous membrane (Fig. 3) but also on some displaced glands.

For the most part *Enterobius vermicularis* found buried is in an early stage of development; it is more difficult to find in the sections an adult worm completely covered by the upper layer because the continuity of the semisquamous epithelial layer is generally broken during the worm's pre-mortem contractions.

Enterobius vermicularis is able to establish itself in the whole of the appendicular organ; it can occupy the space of the mucous membrane (Fig. 4); burrow underneath it (Fig. 5); parasitize the middle of a lymphoid follicle (Fig. 6); or it can invade the peritoneal appendicular layer forming a cyst (Fig. 7). In one of our cases the *Enterobius* was accompanied by the remnant of the carapace of a crustacean (*Cyclops*, fam. *Copepoda*) often found in the drinking water of this city (Fig. 8). We were quite sure that this finding was a genuine one because the cructacean remnants were surrounded by diapedesic cells from the organ.

The different tissues of the appendix showed no undue cellular reaction towards the *Enterobius*, as if

FIG. 1.

FIG. 3.

FIG. 1.—Fresh appendix showing lumen with extensive parasitosis. ×17.

FIG. 2.—Appendix fixed by formol-vapour showing three *Enterobius*. Haematoxylin and eosin. ×150.

FIG. 3.—Appendix fixed by formol-vapour showing larger magnification of a field with two layers of *Enterobius*, some in contact with displaced glands. Notice the cellular structure of the covering layer. Haematoxylin and eosin. ×200.

FIG. 2.

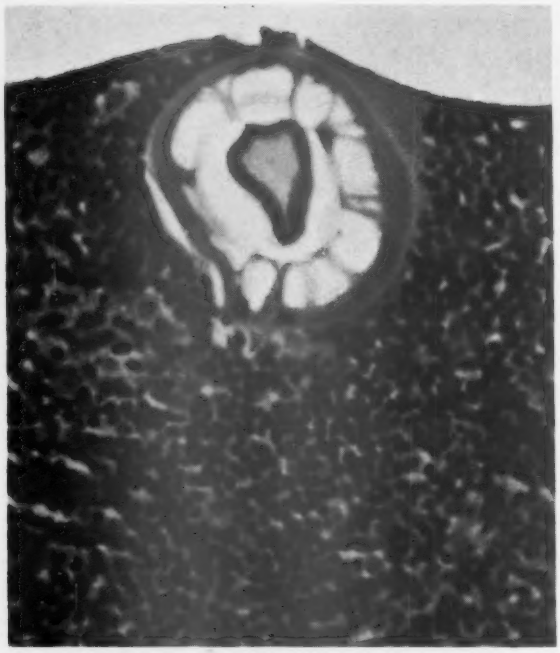

FIG. 4.

FIG. 5.

FIG. 4.—Appendix fixed by formol-vapour. *Enterobius vermicularis* buried in the area topographically belonging to the mucous membrane.

FIG. 5.—Appendix fixed by formol-vapour. *Enterobius vermicularis* buried under the mucous membrane. Notice the keratinous edges and channel built by the appendicular cells. Haematoxylin and eosin. ×200.

FIG. 6.—Appendix fixed by formol-vapour. *Enterobius* buried in the middle of a lymphatic nodule. Notice the continuity of the semi-squamous epithelial layer. Haematoxylin and eosin. ×80.

FIG. 7.—Appendix fixed by formol vapour. Cyst in the peritoneal appendicular layer with an *Enterobius vermicularis*. Haematoxylin and eosin. ×116.

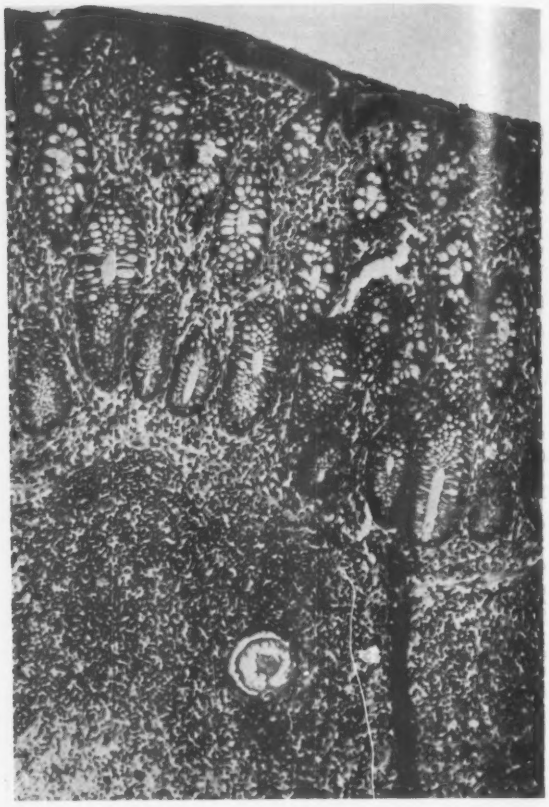

FIG. 6.

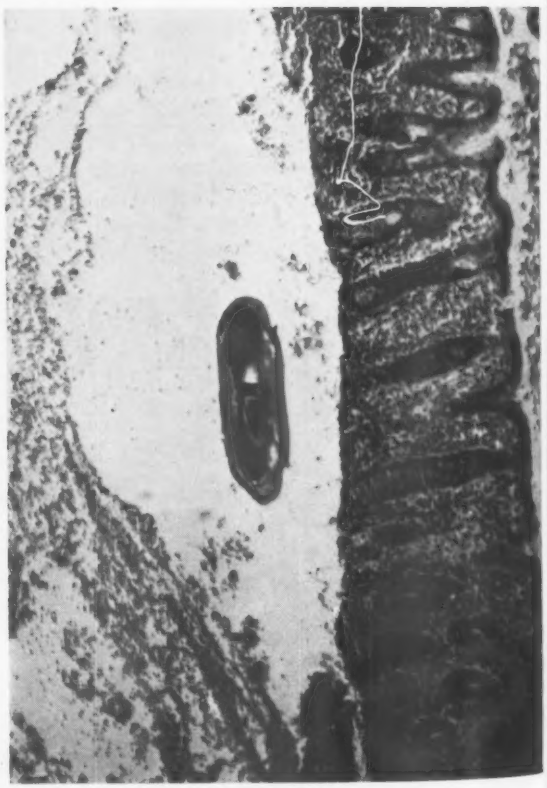

FIG. 7.

the organ and the parasite had been able to establish a perfect symbiotic relationship.

A careful study of *Enterobius vermicularis* shows in its head a double fin-like formation called alae (Fig. 9) from which two very well developed keratinous structures run parallel to the sides of its body. These keratinous structures are serrated (Fig. 10) and when the worm is cut transversally show two very sharp edges similar to a double-edged dagger. The strength of these keratinous structures is demonstrated by the canal built around them by the appendicular cells that house them (Fig. 5). When a fully developed *Enterobius vermicularis* filled with ova is seen buried in the superficial layer it produces an imprint of its irregularities on the top surface of the mucous membrane which shows a perfect replica of the shape of the edge of the worm (Fig. 11). The *Enterobius* also appears to moult (Fig. 12), leaving behind an extra keratinous cover before beginning its long journey to the anus.

Thus it appears that the appendix suffers mechanical damage on two occasions: when the larva leaves the ovum and burrows into the appendicular semi-squamous epithelial layer in search of a place to develop to adult stage in comfort, and again when the individual parasite has reached full maturation, freeing itself and emigrating, full of ova, to the anus. It seems that during these two migratory stages the organ is in great danger of infection from the intestinal flora in its lumen.

Frequency of Infestation in Children

The assessment of parasitosis in the appendices was studied on a histological basis and, therefore, our figures are smaller than those of other authors who have studied the presence of ova or parasites in the appendicular lumen by scraping its surface (Schenken and Moss, 1942).

Of the 691 appendices (400 in boys, 291 in girls), 52 showed positive findings (7·5%); in the 400 appendices of the boys, 19 (4·7%) were positive and in the 291 appendices of the girls 33 (11·3%) were positive. These figures demonstrate that appendicitis occurred more frequently in boys than in girls (1·3 to 1), but that enterobiasis was found to have a more than double frequency in girls than in boys (11·0% to 4·7% respectively).

It was after these results that we decided to carry out a survey of the frequency of infestation in

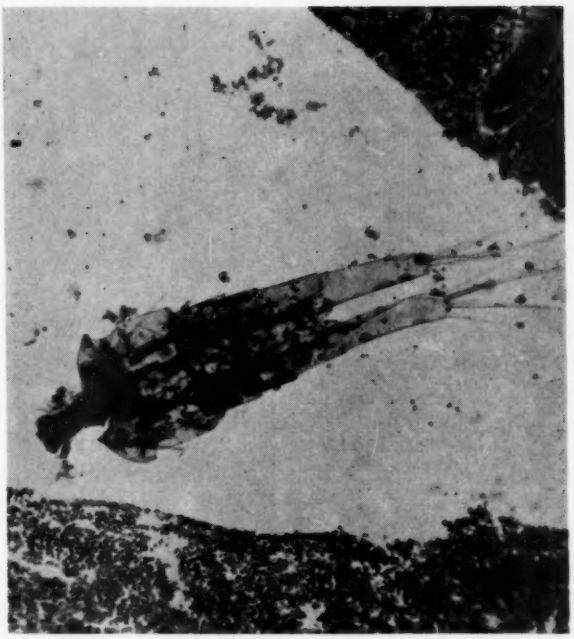

FIG. 8.

FIG. 9.

FIG. 8.—Appendix fixed by formol-vapour. Serial section of the appendix from Fig. 7 showing remnants of the skeleton (carapace) of a crustacean (*Cyclops*, fam. *Copepoda*) often found in drinking water. Haematoxylin and eosin. ×150.

FIG. 9.—A female *Enterobius vermicularis* in fresh preparation showing its alae and keratinous body sides. ×100.

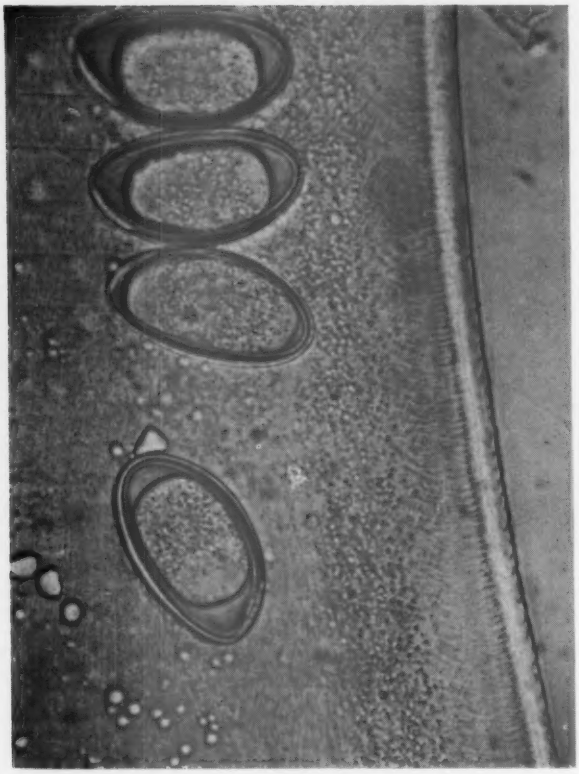

FIG. 10.—A female *Enterobius vermicularis* in fresh preparation showing the serrated aspect of the edge of its body. ×230.

FIG. 11.—Appendix fixed by formol-vapour. Detail of the lower part of an *Enterobius vermicularis* showing the imprint of its edge in the large cellular structure surrounding it. Haematoxylin and eosin. ×200.

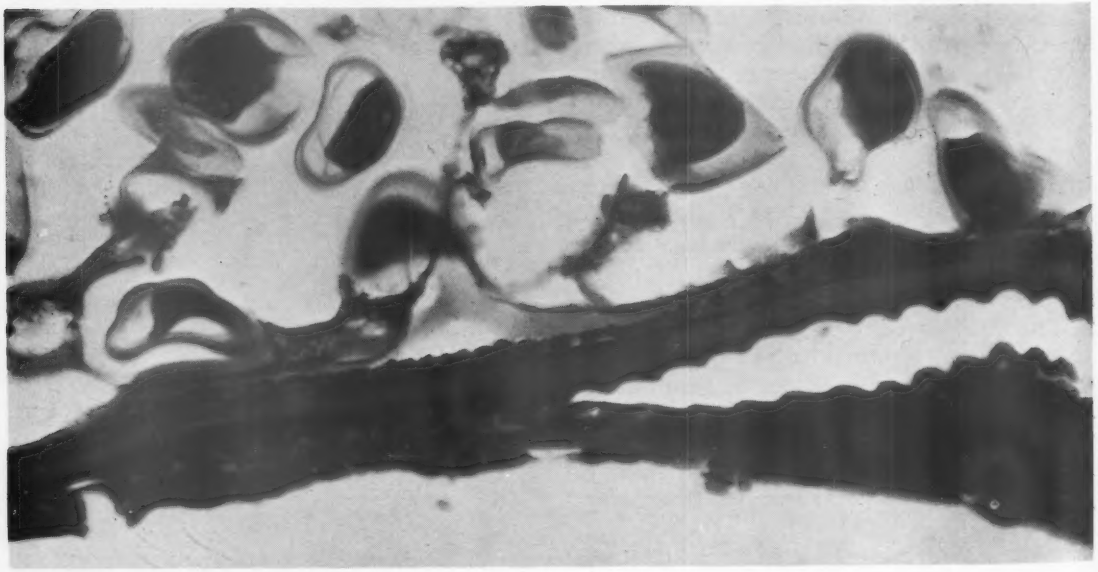

FIG. 12 —Appendix fixed by formol-vapour. Detail of the upper part of the *Enterobius vermicularis* of Fig. 11 showing the moulting of an extra keratinous cover. Notice the cellular aspect of the semi-squamous epithelial layer. Haematoxylin and eosin. ×300.

FIG. 13.—Scotch tape illuminated by a mercury vapour source of light showing the primary fluorescence of an ovum of *Enterobius vermicularis*. Wood's filter. ×200.

children. Two hundred patients already in the wards were examined by the Scotch tape method (Hall, 1937) and later a further 100 cases were examined. Each slide was investigated using a projecting microscope against a screen of 8 in. diameter which gave us the opportunity of studying the whole of the tape adhered to the glass slide without undue fatigue. With a mercury vapour lamp as the source of illumination we found that the ova of *Enterobius vermicularis* showed a primary fluorescence which was confirmed by filtering the light with a Wood's filter, a phenomenon which eased the detection of the ova (Fig. 13). Studying the source of fluorescence in the ova by spectroscopy, it appears that it contains a chromatogen with a maximum of light absorption in the region of the violet band.

The results of the 300 examinations were as follows: boys 164, parasitized 40 (24%); girls 136, parasitized 41 (30%) (Fig. 14). In order to obtain a better understanding of the frequency of infestation in children, we divided them into three age groups: from 0 to 5 years, from 5 to 11 years and from 11 to 16 years, and these results are also shown in Fig. 14. It can be seen that during the critical school years from 5 to 11 the girls showed an increased

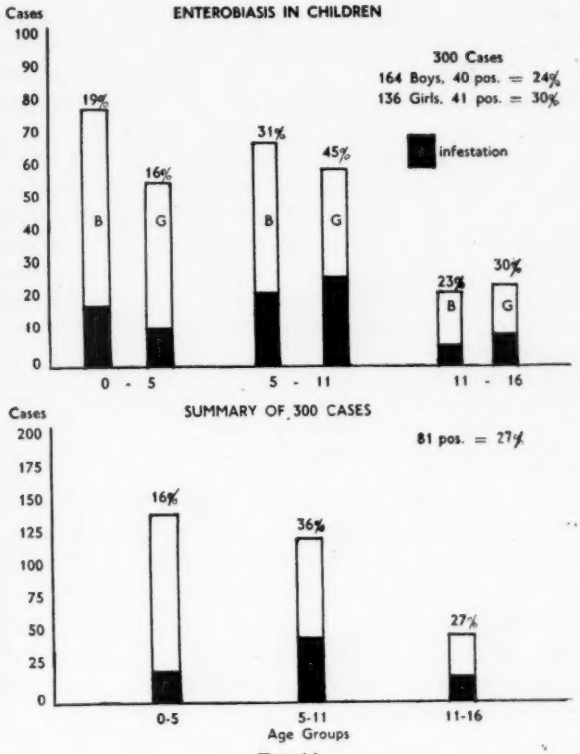

FIG. 14.

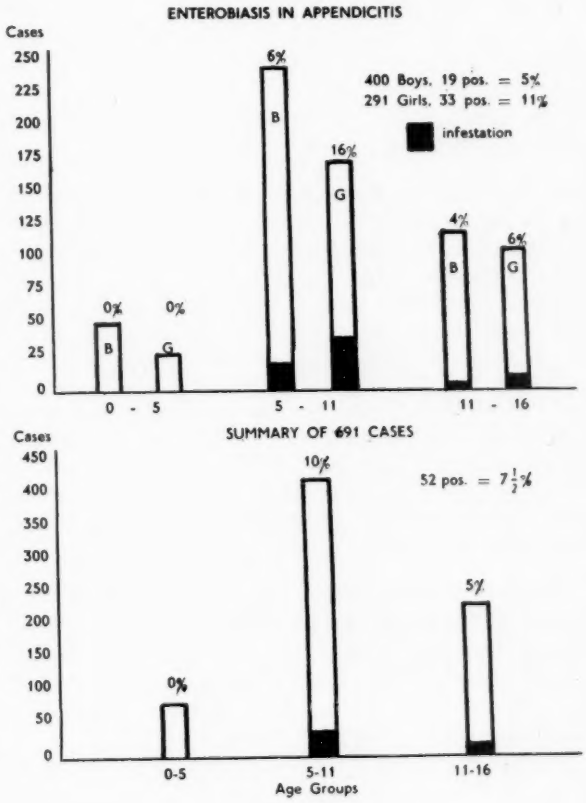

FIG. 15.

percentage of 45% as against 31% in the boys, thereby pointing to the danger held by the lavatory seat for the girls in the primary school. The total incidence of *Enterobiasis* in the 300 cases was 27%.

If the appendicectomized children are now divided into school age groups a more realistic view can be obtained (Fig. 15). No parasitosis of the appendix was found in boys and girls under 5, but in the 5-11-years group we found 237 boys with 14 positives (5·9%) and 170 girls with 27 positives (15·9%). These results correspond with the higher rate of infestation in girls, although the incidence of appendicitis is greater in boys.

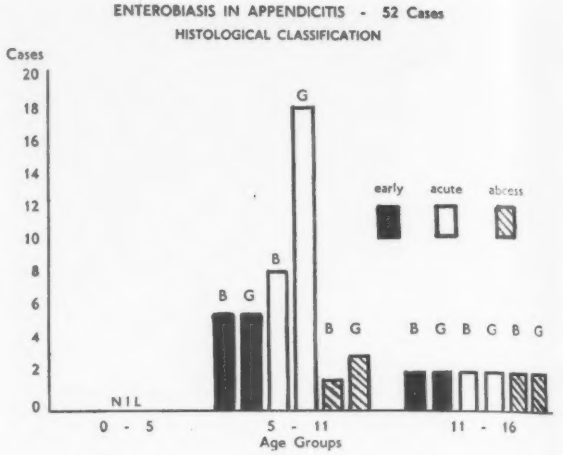

FIG. 16.

Pathology

The full length of the appendices was examined microscopically, the pathology being studied according to any abnormal change, irrespective of extension of area. Our classifications were as follows:

Normal Appendix. The semisquamous epithelial layer would be seen formed only by 'one cell' thickness. Normal glandular morphology and no hyperaemia or cellular infiltration in any layer of the organ.

Early Appendicitis. In this condition there was seen a multicellular thickness epithelial layer with diapedesic cells and red blood corpuscles. The mucous membrane and other layers would sometimes show patches of interglandular hyperaemia or small haemorrhagic areas also.

Acute Appendicitis. A large cellular infiltration of the semisquamous epithelial layer was seen with granulocytes and red blood corpuscles, some areas of clotted plasma, congested or haemorrhagic mucous membrane infiltrated by granulocytes, with the other layers of the organ showing the same infiltration.

Appendicular Abscess. No semisquamous epithelial layer was present but the mucous membrane was destroyed with substitution by a large accumulation of granulocytes occupying part of the appendicular lumen, all other layers of the organ being very congested and infiltrated by granulocytes.

Chronic Appendicitis. The covering layer was monocellular or non-existent with patches of clotted plasma forming small ulcers in the areas where the mucous membrane had disappeared; atrophied mucous membrane formed by one layer of glandular cells; large areas of lymphocytes.

Using the above classifications no normal appendices were found in the 52 cases with enterobiasis; 14 were classified as early appendicitis; 30 as acute appendicitis and eight as showing appendicular abscesses. The division of these results into age groups and sexes is shown in Fig. 16.

Discussion

The problem of enterobiasis and its relationship to appendicitis is a very old one (Garrod and Fairbank, 1907). Some authors, finding the *Enterobius* burrowed in the structures of the appendix, believed that the parasite moved into them as a result of a post-operative phenomenon (Gordon, 1933), but no consideration was given to the need of having an 'untouched' appendix fixed with a technique that shows the whole structure of the organ, together with the material deposited or already existent in its lumen. Only then could it be realized that the invasion of the organ was a genuine one and not the result of faulty histological technique.

We believe that *Enterobius vermicularis* seeks cover and protection against the digestive juices and peristalsis in the appendicular structures and uses its alae to plough a burrow. Our view is supported by the fact that other *Enterobius* infesting some mammals, especially the one found in the hare (*Oxyuris ambigua*), take shelter in the intestinal wall (Penso, 1932). Other helminths which parasitize the gastro-intestinal mucosae of herbivora (cow, sheep, horse) also penetrate them. Therefore, the mechanism of human parasitosis described explains the danger to which the appendix is subjected during the double migratory life of *Enterobius vermicularis* which breaks the defences of the mucous membranes and twice opens them to infection, and it is possible that these migratory phases are manifested by

abdominal pains or by a complete appendicular syndrome.

Apart from this the histological picture of *Enterobius vermicularis* buried in the organ appears to be free of any cellular inflammatory changes as if, during its development *in situ*, it has established a perfect symbiosis.

The penetration into the intestinal wall may also explain the difficulty experienced in actually reaching the parasite with the use of anthelmintics which act locally in immediate contact with the *Enterobius* (Dowsett and Brown, 1953).

Our histological and morphological findings warrant greater consideration of the role played by *Enterobius vermicularis* in appendicitis than hitherto. In this study no normal appendix was found to be parasitized by *Enterobius vermicularis*. However, the study on the incidence of enterobiasis on the one hand and the frequency of appendicitis with its paradoxical results on the other, leaves the problem of the relationship between *Enterobius* and appendicitis still unsolved.

Summary

The preparation with formol-vapour fixation of 691 appendices demonstrated the relationship of *Enterobius vermicularis* with the different appendicular structures. A double migratory phase in the life cycle of *Enterobius vermicularis* is postulated—from the lumen into the organ in the larval stage, and from the organ into the lumen when the nematode has reached full maturation after passing through the stage of moulting.

The incidence of enterobiasis in 300 in-patient children has been analysed, dividing the results into three age groups. Parasitosis was present most often in girls of primary school age. These figures were compared with the incidence of enterobiasis in appendicitis in similar age groups. As the ova of *Enterobius vermicularis* show a primary fluorescence the use of a mercury vapour lamp as a source of light can be used with advantage for their detection.

This study would not have been possible without the enthusiasm of the surgical staff of this hospital, especially Mr. A. Forman, Mr. K. H. Smith, Mr. E. J. Peterson and Mr. V. Kritzinger; the collaboration of physicians for permitting the use of their patients; and the nursing staff for the collection of swabs, and especially Sister M. Foster in theatre for preparing the appendices after removal.

Thanks are also due to Mr. J. D. Joseph, A.R.I.C., F.C.S., Chief Chemist, Manchester Waterworks, for the identification of the crustacean; to my staff for the numerous sections and photographs, and to the Hospital Board of Management for a grant from the Endowment Fund towards expenses.

References

Dowsett, L. M. and Brown, A. E. (1953). *Lancet*, **1**, 1070.
Duran-Jorda, F. (1946). *Brit. J. Surg.*, **33**, 346.
Garrod, A. E. and Fairbank, H. A. T. (1907). *Lancet*, **2**, 772.
Gordon, H. (1933). *Arch. Path.* (*Chicago*), **16**, 177.
Hall, M. C. (1937). *Amer. J trop. Med.*, **17**, 445.
Penso, G. (1932). *Ann. Parasit. num. comp.*, **10**, 271.
Schenken, J. R. and Moss, E. S. (1942). *Amer. J. clin. Path.*, **12**, 509.

EPIDERMOLYSIS BULLOSA HEREDITARIA 'LETALIS': REPORT OF A CASE SURVIVING FOR TWO AND A HALF YEARS

BY

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Epidermolysis bullosa is a chronic hereditary disease of unknown aetiology involving the skin and mucous membranes. It is characterized by the formation of multiple superficial vesicles and bullae which develop spontaneously or as a result of minimal trauma. The disease may occur in varying grades of severity but there is one form with distinct characteristics which has been classified as epidermolysis bullosa hereditaria letalis. In all other cases it has been uniformly fatal within the first few months of life. The purpose of this paper is to report a patient who has this type of the disease but is still alive at the age of 30 months.

Case Report

S.B. was born at term at the Grace-New Haven Community Hospital after an uneventful pregnancy. She was the third child of a 24-year-old white woman whose serological tests for syphilis were negative. The first pregnancy had resulted in a mentally retarded female with a convulsive disorder and the second in a female with congenital heart disease. Inquiry regarding the occurrence of a similar skin condition in the parents, grandparents, great-grandparents and other members of the family failed to reveal any significant abnormalities in any of them. There was nothing in the story of either parent to accord with the fact that all their four children had congenital abnormalities. At birth the patient appeared normal except for numerous bullous and denuded areas on various parts of her body, including the dorsum of the right foot, right calf, several toes, lips and the mucous membranes of the mouth and nose.

Immediately after birth, the infant was transferred from the delivery room to a nursery and strictly isolated. She was placed in an open crib lined with plastic sheeting. She was kept unclothed with the covers raised above her body in an attempt to minimize irritation to the skin. Body warmth was maintained with the aid of a goose-necked heat lamp. She was handled as little as possible, and then only by persons who wore gown, mask and sterile gloves. Within the first six hours of life the first of several antibiotics was started in an attempt to prevent and eliminate secondary infections of the open lesions. Various methods of feeding were tried, including medicine dropper, gavage, nipple and medicine glass. In spite of these measures new lesions appeared on the trunk, head, extremities and mucous membranes. The lesions would begin as localized areas of erythema which became bullous, sloughed and would then gradually granulate and epithelialize. When one of the bullae broke, a crust formed which sealed off the denuded portion of the skin so that fluid loss from the lesions was never very extensive. Scarring did not occur although a residual area of erythema might persist for many weeks. Bullae in the mouth were frequently haemorrhagic, while those of the skin occasionally contained blood-tinged fluid.

Because of the known severity of the disease process and the expected fatal outcome, it was decided to try various hormones in an attempt to alter the course of the disease. On the thirty-second day of life she was started on a preparation of conjugated oestrogens, 0·625 mg. daily. One week later this was discontinued and hydrocortisone, 20 mg. every eight hours, orally, was given. Four weeks later the dosage of hydrocortisone was increased to 20 mg. every four hours. After 10 days on this dosage she was gradually weaned from this drug. At the age of 2½ months she was given testosterone propionate, 5 mg. daily, for one week. Although fewer lesions seemed to be appearing during the second month of life, hormone therapy did not produce any marked change in her course.

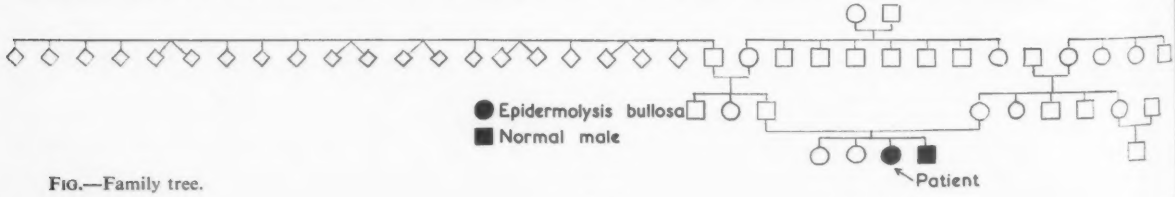

FIG.—Family tree.

At 9 weeks of age an abscess developed on the right ankle. This required surgical drainage and then subsided without complication. Non-haemolytic staphylococcus was cultured from the abscess.

For the next nine months her condition remained essentially unchanged. New lesions continued to appear which would go through a full cycle and then heal without leaving any scars. When she was 7 months old the aseptic technique and strict isolation were gradually liberalized in order to permit freer handling and increased social contact. During the summer months she was kept in an air-conditioned room to prevent marked swings in environmental temperature. At 10 months of age when her condition seemed stable she was transferred to a nursing home.

For the next 20 months the disease process continued to be active. New lesions appeared on all parts of the body and in the mouth. Occasionally these would become secondarily infected and as a result almost continuous antibiotic therapy was necessary. Several nails were lost completely and in these areas epithelialization occurred but no deformities resulted. Development was slow although she was able to say a few words. Her spirits were usually good but she became irritable when handled by strangers. Her weight gain was relatively slow. She had been found to have an iron-deficiency anaemia at the age of 1½ years and had been given treatment with supplemental iron. No special isolation precautions were being used. At the age of 2½ years her condition continued to be essentially unchanged.

When the patient was 21 months old the mother gave birth to a 3,120 g. boy who also had epidermolysis bullosa. At birth several denuded areas were present on the lower extremities. During the first few days of life he developed new lesions on the extremities, face and in the mouth, which were identical with those that his sister had had. When these eventually cleared there was no residual scarring of the skin. He was started on prophylactic antibiotics shortly after birth and received the same type of nursing care that was administered to his sister. In addition he received cortisone, 100 mg. daily, from the third to twentieth day of life, and prednisone, 20 mg. daily, for an additional six days. Although his disease was extensive, it was not felt to be as severe as it had been in his sister. At the age of 2 months he developed a staphylococcus pneumonia which responded well to chloramphenicol and novobiocin. After recovery from this infection he was transferred to a nursing home.

Discussion

Epidermolysis bullosa was first described by von Hebra in 1870 and by Fox in 1879 and was given its present name by Köbner in 1886. It usually affects infants at birth or shortly thereafter, but may not appear for months or even years. The disease is characterized by multiple vesicles or bullae which are most apt to occur at the sites of pressure or trauma. The bullae may be filled with a clear serous material or with blood-tinged fluid which is sterile on culture. In certain forms of epidermolysis bullosa the mucous membranes of the alimentary and respiratory tracts are involved. The finger- and toe-nails are frequently thickened and deformed or they may be absent. In many, but not all of the cases, Nikolsky's sign (detachment of the upper layers of the skin by trauma) may be present.

Several theories as to the aetiology of the disease have been postulated. These include endocrine imbalance, increased irritability of the cutaneous vascular system (Elliot, 1900), absence or deficiency of elastic fibres in the papillary and subpapillary layers of the skin (Engman and Mook, 1906), a disturbance of the vascular system with some inherent defect of the vessel wall itself (Winer and Orman, 1945) and an altered hyaluronidase-heparin ratio (Langhof, 1952). However, the most widely accepted theory is that there is some inherited intrinsic disturbance of the structure of the skin.

The pathological findings have been quite variable. Herlitz (1935) reported that the skin was unusually thin and showed degeneration of the elastic fibres with rudimentary sweat glands and hair follicles. Engman and Mook (1906), Matheson and Rosner (1949), Siemans (1937) and Schäffer (1951) also concluded that the superficial layers of the skin contained deficient elastic tissue, while Leland and Hirschl (1954) observed degeneration of the collagen fibrils of the skin. On the other hand Lamb and Halpert (1947) found the hair follicles, sebaceous and sweat glands and collagenous bundles in the skin to be normal, and Lewis, Steven and Farquhar (1955) noted apparently normal elastic elements in two fatal cases.

Epidermolysis bullosa has been divided into four main forms (Herlitz, 1935; Cockayne, 1933; and Touraine, 1942).

(1) Simple, Non-scarring Type. This is a simple non-scarring type which appears in infancy or childhood in otherwise normal children and is inherited as a Mendelian dominant trait. This form is manifested by superficial bullae which develop mainly over the extremities as a result of friction or trauma. The bullae heal within a few days without scarring or pigmentation. The mucous membranes and nails are not involved. The disease is usually self-limited and tends to improve markedly or to disappear completely at puberty.

(2) Mendelian Dominant Type. A Mendelian dominant dystrophic type is transmitted by affected members of either sex and appears at birth or soon afterwards in children who otherwise have normal physical and mental development. The lesions are particularly severe on the hands or toes and over

CLINICAL CLASSIFICATION OF EPIDERMOLYSIS BULLOSA

Type	Mendelian Inheritance	Age of Onset	Site of Lesions				Persistence of Lesions	Residual Scarring	Physical Development	Mental Development	Prognosis
			Extremities	Mucous Membranes	Nails	Trunk					
Simple or non-scarring	Dominant	Infancy or childhood	+	0	0	0	Few days	0	Normal	Normal	Clears at puberty
Dystrophic (dominant)	Dominant	Birth or early infancy	+	±	+	±	Prolonged	+	Normal	Normal	May clear at puberty
Dystrophic (recessive)	Recessive	Birth or early infancy	+	+	+	±	Prolonged	+	Retarded	Retarded	Most die in childhood
Lethal (Herlitz)	Recessive	Birth or neonatal	+	+	+	+	Prolonged	0			Most die in early infancy
Present case	Unknown	Birth	+	+	+	+	Prolonged	0	Retarded	Retarded	Alive at 2½ years

other areas liable to trauma or pressure. The lesions may heal without scarring, but in many instances thin atrophic scars are formed which contain small epidermal cysts. Finger- and toe-nails are often lost and on growing back may be thickened or deformed. The mucous membranes may be involved and when lesions in these areas heal a leukoplakia-like atrophy results. This form of the disease sometimes improves spontaneously at puberty but the abnormal traumatic response may persist throughout life.

(3) Recessive Dystrophic Type. A recessive dystrophic type appears at or shortly after birth and affects children who subsequently have poor physical and mental development. Bullae are formed which are often large and filled with blood-stained fluid. On healing, keloidal scars, contractures and pigmentation may occur. The finger- and toe-nails and the mucous membranes of the alimentary and respiratory tracts are frequently affected. There may be associated congenital defects of teeth, nails and hair. Many of these children die in infancy and it is very unusual for any to reach maturity.

(4) Lethal (Herlitz) Type. A lethal (Herlitz) type is transmitted as a Mendelian recessive and appears at birth or shortly thereafter. It is characterized by the appearance of multiple superficial bullae not specifically related to trauma which often contain blood-stained fluid. There is marked deformity of the finger- and toe-nails and some of these nails may be missing. The mucous membranes are uniformly involved with bullous lesions which break and leave ulcerations. Nikolsky's sign may be present. The lesions heal without scarring. Skeletal atrophy may occur near areas of skin showing localized congenital defects.

Herlitz (1935) first classified this as a distinct type and called it 'epidermolysis bullosa hereditaria letalis'. He reported eight cases of his own and collected 14 others from the literature. In 1954 Leland and Hirschl reviewed this form of the disease and found a total of 34 cases. They added two more of their own in twin mulatto females. Since then other cases have been reported by Frank and Kern (1954), Calnan (1954-55), Lewis *et al.* (1955) (three cases), Henderson (1955) (four cases) and Lucini (1955), making a total of 46 cases.

The patient herein reported had the main features of the variety of epidermolysis bullosa first described by Herlitz. Her disease started at birth and was characterized by vesicles and bullae involving the skin and mucous membranes. Many of the bullae were haemorrhagic and those on the buccal mucosa often became ulcerated. Severe lesions occurred around the finger- and toe-nails and this resulted in marked deformity or complete destruction of these structures. In spite of the extensive involvement of the skin, lesions healed without scarring.

The lethal form of epidermolysis bullosa was originally thought to result in death within the first three or four months of life. However, several cases, including those of Calnan (1954-55) and Henderson (1955), have lived for at least six months, and one of the patients reported by Kagen, Williams, Giffin and Wiley (1952), which in other respects appeared to be a typical case of epidermolysis bullosa hereditaria letalis, lived to the age of 16 months. Our patient is alive at the age of 30 months, and even though the disease process continues to be active,

it is not as severe as during the first weeks of life. She exhibits both physical and developmental retardation, but these may be due, in part, to the restriction of activity that has been necessary during a large part of her life.

Since it was our impression initially that we were dealing with a rapidly fatal disease, the empirical use of various forms of therapy seemed to be indicated in the hope that they might alter the expected course. Immediately after birth the child was isolated in a room by herself and placed in an open crib lined with plastic sheeting. She was handled as little as possible and then only by those who wore gowns, masks and sterile gloves. Various antibiotics were given singly or in combination in an attempt to prevent and eradicate secondary infections. Since the improvement occurring at puberty in certain mild types of epidermolysis bullosa may take place as a result of increased amounts of adrenal, ovarian or testicular hormones being produced at that time, therapy with such preparations was felt to be justifiable in our patient. Accordingly, during the second and third months of life, she was given courses of conjugated oestrogens, hydrocortisone and testosterone. No control periods of observation were carried out and we were unable to evaluate definitively the relative effectiveness of these drugs. Although the hormones may have played a role in altering the course of her disease, it was our clinical impression that meticulous nursing care, scrupulous isolation technique and the antibiotics that were used were extremely important. In addition an inherent difference between the severity of the disease process in our patient and those previously reported may have contributed materially to her survival.

Summary

A child with epidermolysis bullosa hereditaria 'letalis' who is still alive at 30 months of age is reported.

Various forms of therapy were tried. It was felt that the survival of the patient for two and a half years, in contrast to all others previously reported who had died before the age of 16 months, was due either to an inherent difference in the disease process and/or to the careful nursing care, scrupulous isolation technique and antibiotic and hormone therapy that was used.

References

Calnan, C. D. (1954-55). *Gt Ormond Str. J.*, No. 8, p. 113.
Cockayne, E. A. (1933). *Inherited Abnormalities of the Skin and its Appendages*, p. 118. London.
Elliot, G. T. (1900). *N.Y. med. J.*, **71**, 585.
Engman, M. F. and Mook, W. H. (1906). *J. cutan. Dis.*, **24**, 55.
Fox, T. (1879). *Lancet*, **1**, 766.
Frank, D. J. and Kern, W. H. (1954). *Ohio St. med. J.*, **50**, 679.
Hebra, von (1870). Cited by Matheson, A. and Rosner, D. C.
Henderson, A. T. (1955). *J. Pediat.*, **46**, 186.
Herlitz, G. (1935). *Acta paediat. (Uppsala)*, **17**, 315.
Kagen, M. S., Williams, L., Giffin, W. and Wiley, R. (1952). *Wis. med. J.*, **51**, 766.
Köbner, H. (1886). *Dtsch. med. Wschr.*, **12**, 21.
Lamb, J. H. and Halpert, B. (1947). *Arch. Derm. Syph. (Chicago)*, **55**, 369.
Langhof, H. (1952). *Derm. Wschr.*, **126**, 764.
Leland, L. S. and Hirschl, D. (1954). *A.M.A. J. Dis. Child.*, **87**, 321.
Lewis, I. C., Steven, E. M. and Farquhar, J. W. (1955). *Archives of Disease in Childhood*, **30**, 277.
Lucini, E. (1955). *Lattante*, **26**, 38.
Matheson, A. and Rosner, D. C. (1949). *Amer. J. Dis. Child.*, **78**, 708.
Schäffer, G. (1951). *Acta derm.-venereol. (Stockh.)*, **31**, 704.
Siemens, H. W. (1937). *Arch. Derm. Syph. (Berl.)*, **175**, 590.
Touraine, A. (1942). *Ann. Derm. Syph. (Paris)*, 8 ser., **2**, 309.
Winer, M. N. and Orman, J. M. (1945). *Arch. Derm. Syph. (Chicago,)* **52**, 317.

VACCINIA GANGRENOSA AND AGAMMAGLOBULINAEMIA

BY

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Normally, primary vaccination against smallpox produces a vesicle on an inflamed base in four days, enlarging for a further five days with umbilication, and healing under a scab in about three weeks. Pyogenic infection of the primary lesion is the most common complication of vaccinia. Secondary vaccinal lesions may occur as the result of auto-inoculation of adjacent or distant areas of skin. The lesions are scanty and their distribution asymmetrical with a minor constitutional reaction. When more numerous and symmetrically distributed, there is malaise and fever indicating a generalized vaccinia. Its incidence is estimated at about 1 in 25,000 vaccinations (Blank and Rake, 1955), and the lesions, appearing one or two weeks after vaccination, resolve with the primary 'take'. A serious type of generalized vaccinia occurs in the presence of pre-existing skin disease, particularly eczema, and is a variety of Kaposi's varicelliform eruption, better called eczema vaccinatum. The prognosis in this rare complication used to be very serious, but with modern treatment is not so.

Approximately 1·78 million persons of all ages, of whom 1·05 million were under the age of 1 year, were primarily vaccinated in England and Wales under the National Health Service, during the five-year period 1950-54 (Ministry of Health, Annual Reports of the Chief Medical Officer, 1950-54). Of these, the complication of generalized vaccinia was notified in 78 cases (four notified cases of generalized vaccinia after re-vaccination are for obvious reasons excluded), an incidence of 1 in 22·9 thousand primary vaccinations at all ages. Of the total number, six were cases with pre-existing eczema, i.e., eczema vaccinatum, of which two were fatal. Only two cases of generalized vaccinia, in the absence of pre-existing skin disease, died. The one, a girl, aged 4 months, was reported by Laurance, Cunliffe and Dudgeon (1952) as a case of vaccinia gangrenosa; the other was a female infant who died presumably from the same complication on the forty-third day after primary vaccination (Ministry of Health, Annual Report of the Chief Medical Officer, 1952). In all other cases, recovery was rapid and complete.

Rare instances of severe similar forms of generalized vaccinia have been reported from time to time. Hutchinson (1879) first described a fatal case of gangrene of skin following vaccination, and he applied the term 'vaccinia gangrenosa' to his case and to that of Stokes (1880). More recently a total of 13 cases of vaccinia gangrenosa have been reported: (Acland and Fisher (1893); Shortt's case (Shortt, 1933) later detailed by Dible and Gleave (1934); Bigler and Slotkowski (1951); the case reported by Laurance *et al.* (1952) and later by Hall, Cunliffe and Dudgeon (1953); Laurance *et al.* (1952) mention three other cases of which they had personal communications; Keidan, McCarthy and Haworth (1953); Kozinn, Sigel and Gorrie (1955) reported another and mentioned four other cases, one of which was ascribed to Barbero, Gray, McNair Scott and Kempe (1954, 1955).)

Of the total number, the only authentic case of recovery was that of Barbero *et al.* (1954, 1955). The other reported case of recovery, mentioned by Laurance *et al.* (1952) and quoted by Keidan *et al.* (1953), was assumed for some reason or other to have recovered from the vaccinal lesions. On closer examination, however, it seems probable that the patient's death was related to vaccinia gangrenosa (Dudgeon, 1956).

Keidan *et al.* (1953) first reported agammaglobulinaemia in a case of vaccinia gangrenosa. The patient, a girl, was vaccinated at the age of 8 weeks, and died seven weeks later, after being unsuccessfully treated with post-vaccinal serum and intramuscular injections of gamma globulin. The second case is mentioned by Kozinn *et al.* (1955) together with the third described by them in a 3-month-old male with extensive metastatic lesions, which was also fatal despite intramuscular injections of gamma

globulin, intravenous infusions of post-vaccinal plasma, antibiotics and also A.C.T.H. and cortisone. The infant died approximately four weeks after primary vaccination.

The case reported here is the fourth case of vaccinia gangrenosa associated with agammaglobulinaemia.

Case Report

History. A boy born on August 5, 1955, was admitted on February 13, 1956, aged 6 months, having been referred to The Hospital for Sick Children because of persistent unhealed primary and disseminated vaccinal lesions.

He was the third child of healthy parents. The pregnancy, birth and neonatal growth and development had been normal. The birth weight was 7 lb. 14 oz. He was breast-fed for two months and then changed to 'ostermilk' No. 2, on which he continued to thrive. There was no past history of infections or other illnesses. On direct questioning, however, the parents thought his skin had been somewhat dry since the age of 5 weeks, but there had been no obvious suggestion of infantile eczema.

Both parents and two sisters aged 9 and 7 years had been successfully and uneventfully vaccinated. The parents came from large healthy families. The mother's family was southern English, the father's family Irish. As far as it could be checked, there had been no family history of recurrent infections or deaths in infancy or childhood.

At the age of 12 weeks he was vaccinated on the right deltoid region at a local clinic. The scarification method was used. Two scratches were made, as lymph on the first scratch had been accidentally wiped off. Within a week two apparently normal 'takes' occurred, but the vesicle continued to extend and increase in size and discharged yellow pus. A week later he was seen at a local hospital and chlortetracycline ('aureomycin') ointment was prescribed in the belief that the vaccination had become secondarily infected.

Over the next few weeks, the vaccination sore had extended from the shoulder to the elbow and crops of small vesicles appeared on the forehead, behind the left ear and on the tongue. He went off his feeds, became irritable and developed a fever.

He was admitted to The Hospital for Sick Children 12 weeks after vaccination.

Examination. He was a small, ill-looking, fretful baby weighing 11½ lb., with a temperature of 101·6° F. and pulse 180/minute.

The striking findings were confined to the skin, which showed an eruption of flat plaques with well-defined bullous edges, circumferentially over the whole of the right arm, the left forehead and external ear, the right temple, tip of the nose and upper lip, and a large area of the perineum. Many of the lesions had shown progressive central necrosis resulting in sharply punched-out ulcers with a flat, bright red, granular base, at first covered by a yellowish-brown slough, firmly adherent.

FIG. 1.

FIG. 2.

FIGS. 1, 2.—Appearances 12 weeks after vaccination.

The margins of the necrotic areas were red for a few millimetres, but beyond this no inflammatory reaction was visible in the surrounding skin. There was drooling at the mouth and a circular ulcerated area on the dorsum of the tongue covered with mucopurulent exudate. The morphology of this shallow ulcer conformed closely with that of the skin lesions. The general dermatological picture was that of vaccinia gangrenosa (Figs. 1 and 2).

Examination of the chest was normal. The liver and spleen were palpable one fingerbreadth. No enlarged lymph nodes were evident.

Investigations. A blood count gave: Haemoglobin 58% (8·6 g./100 ml.); W.B.C. 11,800/c.mm. (neutrophils 76%, lymphocytes 16%, monocytes 8%); blood group, A Rh negative.

Bacteriology. Swabs from skin lesions, including the perineum amd dorsum of the tongue, with Gram stain showed debris only. On culture there was a heavy growth of coagulase-positive staphylococci, sensitive to penicillin, streptomycin and chloramphenicol but resistant to tetracyclines and sulphonamides. Fungi were not isolated.

Virology. Dr. J. A. Dudgeon found that smears from vesicular lesions on the perineum showed a few elementary bodies, morphologically similar to vaccinia.

Swabs from the tongue and perineal lesions were heavily infected with coagulase-positive staphylococci and streptococci. Material had to be filtered owing to heavy secondary infection. The filtrate produced vaccinal-like lesions on the developing chick embryo.

Plasma proteins totalled 3·43 g./100 ml.

Electrophoresis. Classical Tiselius and filter paper techniques of electrophoresis failed to show gamma-globulin.

Treatment. After cleansing with normal saline, a lotion of 3% formalin in lot. calamine B.P. was applied to the skin and 3% formalin in glycerine to the tongue. The skin was later treated with 'neomycin' 1% ointment, to which the staphylococci were sensitive.

Chloramphenicol, 25 mg. six-hourly by mouth, was begun in preference to the tetracyclines, because of resistant skin staphylococci.

As soon as the presence of agammaglobulinaemia had been confirmed he was started on intramuscular injections of vaccinia gamma globulin, 250 mg. daily for nine days, totalling 2,250 mg. (22·5 ml.) supplied by the Public Health Laboratory, London.

Three hundred millilitres of compatible group A Rh-negative blood were transfused by a scalp vein and the haemoglobin was raised thereby to 96% (14·2 g./100 ml.).

Progress. Although the skin lesions looked cleaner on treatment, the areas involved continued to extend. Fresh crops of flat-topped vesicles appeared ceaselessly. Swabs taken from them for virology were positive for vaccinia. No lesions developed at sites of venepuncture or intramuscular injection.

The temperature was unabated and after a week began to swing up to 105° F. The baby looked ill and steadily deteriorated. His weight fell from 11½ lb. to less than 10 lb. A hoarse cry developed.

About the sixth day on chloramphenicol he began to pass continuous loose, watery stools. No pathogens were detected on examination. However, chloramphenicol was discontinued and injections of penicillin, 500,000 units, and streptomycin, 125 mg. b.d., to which the skin staphylococci were still sensitive, were begun. Tinct. opii. m 1, eight-hourly did not improve the diarrhoea.

On the tenth day of admission he became jaundiced and drowsy. Liver function tests showed:

Serum bilirubin	4·3 mg./100 ml.
Alkaline phosphatase	13 μ./100 ml.
Thymol turbidity	1 μg.
Zinc sulphate turbidity ..	1 μg.
Blood urea	77 mg./100 ml.

A repeat examination of plasma proteins after treatment with vaccinia gamma globulin showed:

Total proteins	5·43 g./100 ml.
Albumin	2·75 g./100 ml.
Globulin	2·68 g./100 ml.
A/G	1·03

Electrophoresis: Trace of gamma globulin.

Two weeks after admission frank dry gangrene was seen over the right ear lobe. In the next few days he developed moist signs in the chest together with recession and died on the twentieth day of admission, approximately 15 weeks after primary vaccination.

Neutralization tests on serum collected at necropsy (Dr. J. A. Dudgeon) showed slight neutralizing activity to vaccinia virus but considerably less than that shown from a serum of a recently vaccinated person. It seemed probable that the small amount of neutralizing antibody was due to the residual gamma globulin which had been given to the child.

Necropsy Findings. The post-mortem examination was made by Dr. Martin Bodian. Inspection showed the wasted body of a male infant. Numerous well-defined ulcers with flat, reddened bases were noted over the scalp, external ears, tip of the nose, upper lip, right arm and perineum. There was a large, sharply defined ulcer on the dorsum of the tongue.

Both lower lobes of the lungs were consolidated and the other lobes showed small areas of consolidation, some with evidence of central suppuration. The mucosa of the trachea and bronchi was haemorrhagic and covered with a little granular purulent exudate.

The liver was moderately enlarged and the capsular and cut surfaces showed a mottled appearance, reddish-brown areas alternating with cream coloured areas. The lobular pattern was indistinct. The spleen was slightly enlarged, firm and plum coloured. Malpighian bodies were inconspicuous. The capsular and cut surfaces of the kidneys also showed a mottled appearance of alternating reddish-brown and cream coloured areas. The cortico-medullary pattern was well defined. The adrenals showed nothing abnormal.

A well-defined longitudinal ulcer with raised yellow margins was noted at the lower end of the oesophagus. There was considerable gaseous and fluid distension of the small bowel. The mucosa of the jejunum and ileum showed patchy hyperaemia but no ulceration.

The brain was oedematous. The myocardium was pale and flabby.

Gram stain of swabs from the right lower lobe and left bronchus showed polymorphonuclear cells and Gram-positive cocci. Coagulase-positive staphylococci and *Esch. coli* were grown on culture. In addition the bronchial swab grew *Streptococcus faecalis*.

FIG. 3.—Photomicrograph of edge of ulcer of tongue, ×30, showing necrosis of epithelium and scanty cellular response. Numerous 'ballooned' cells, in epithelium adjacent to ulcer. Clumps of cocci on surface of ulcer.

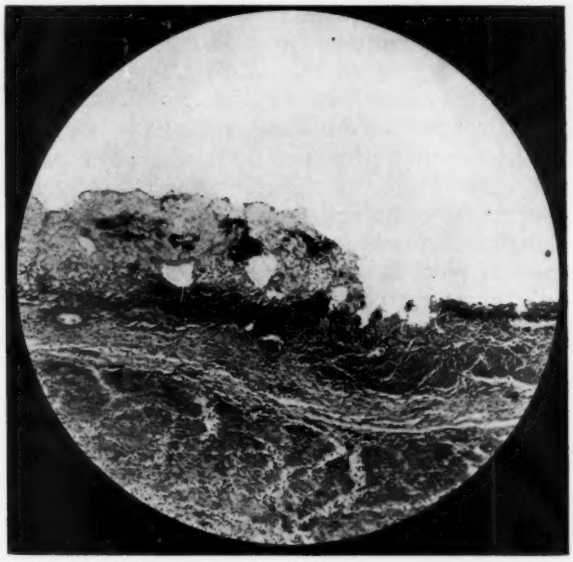

FIG. 4.—Photomicrograph of section of lower oesophagus, ×30, showing edge of ulcer penetrating muscularis mucosae. Little inflammatory cellular response. Clumps of cocci in necrotic debris covering base of ulcer.

Histology. On section the tongue showed extensive mucosal ulceration and infiltration of the subjacent tissue with scanty mononuclear cells. Epithelial cells adjacent to the areas of necrosis showed considerable 'ballooning' and occasionally eosinophilic intracellular inclusion bodies (Fig. 3). A piece of skin from the arm showed hyperaemia and a little mononuclear infiltration of the epidermis as well as ballooning of some cells. Inclusion-containing cells were not seen. The perineal skin showed necrosis of the epidermis and hair follicles with scanty inflammatory cellular infiltration. Occasional epidermal cells contained eosinophilic inclusion bodies. Extensive focal necrosis of the mucosa and submucosa, including the muscularis mucosae and mucous glands, was shown on section of the lower oesophagus. A few adjacent epithelial cells contained eosinophilic inclusion bodies (Fig. 4).

The parenchymal cells of the liver revealed moderate vacuolation due to fatty change but in other respects the liver was normal. In particular there was no focal necrosis. The splenic pulp was congested. The malpighian lymphoid follicles were very inconspicuous and showed a most remarkable paucity of germinal centres. Sections of lymph nodes showed a similar marked reduction in follicles and absence of germinal centres. These changes were presumably associated with agammaglobulinaemia.

The kidneys showed small superficial subcapsular foci of mononuclear infiltration and there was generalized hyperaemia. There was nothing remarkable in the adrenals.

Sections of the lungs showed extensive necrotizing bronchitis and bronchiolitis with peribronchiolar extension of the inflammatory process. The bronchial mucosa was almost completely shed. No inclusion-containing cells were seen (Fig. 5).

There was a slight excess of mononuclear cells in the leptomeninges and the epicardium. The brain and the heart were otherwise normal.

Discussion

The progressive necrotizing vaccinal reaction, failure to heal and the development of gangrene,

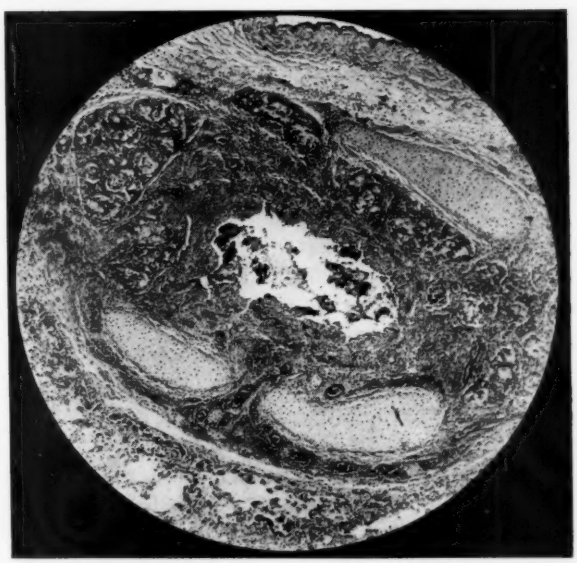

FIG. 5.—Photomicrograph of section of lung, ×30, showing a branch bronchus. Necrosis of epithelium with poor cellular response; lumen filled with debris containing clumps of cocci.

together with the continued appearance of fresh lesions at various sites, were distinguishing features of vaccinia gangrenosa. A severe toxaemia was suggested by jaundice, as evidence of hepatitis, and the baby's profound illness.

There are no criteria to determine which patient will develop a severe form of generalized vaccinia —apart from the patient with obvious pre-existing skin disease, particularly eczema. Of the 14 reported cases of vaccinia gangrenosa (including our patient) only five were checked for the blood content of gamma globulin. All four who lacked it died. Whilst agammaglobulinaemia has been increasingly noted in association with recurrent bacterial infections in childhood (leading article, *British Medical Journal*, 1955), it has been stated that patients with agammaglobulinaemia respond to vaccination without complication in contrast to their undue susceptibility to bacterial infections (Apt, 1953-54). However, the risk of severe vaccinal reaction and death, perhaps ascribable to secondary bacterial infection, is such that it would seem unwise to vaccinate patients with known agammaglobulinaemia, especially as the risk of smallpox is so small in western countries. It is advisable also to test for plasma gamma globulin in all patients with generalized vaccinal reactions.

All but one of the reported cases of primary agammaglobulinaemia have been boys, which points to an inherited sex-linked Mendelian trait. Should the parents of our patient have another male child, the chances of its having agammaglobulinaemia will be 1 in 4. As for the exception, the case described by Keidan *et al.* (1953), it has been suggested that the deficient gamma globulin was not identical with that lacking in the boys (Hutchison, 1955). Agammaglobulinaemia in adolescents and adults of either sex seems to be the acquired variety (*British Medical Journal*, 1955).

Keidan *et al.* (1953) and also Kozinn *et al.* (1955) comment on the absence of enlarged lymph nodes together with a marked reduction of germinal centres in sections of lymph nodes in their cases. These observations have also been borne out in the present case, and in a number of reported cases of agammaglobulinaemia (leading article, *British Medical Journal*, 1955). The congenital inability to synthesize gamma globulin may perhaps be associated with atrophy of lymphoid tissue.

With regard to management, any patient with a generalized vaccinal reaction should be treated with vaccinia gamma globulin, which is now available in pure form for intramuscular injection. Immune plasma or blood from recently vaccinated donors is difficult to obtain and has proved disappointing in use. Larger amounts of vaccinia gamma globulin can be given as the pure substance than as immune plasma or blood. Our patient was given 250 mg. daily for nine days, a course which may be considered adequate in respect of antibodies. With the usual amounts administered, gamma globulin is unlikely to be reflected in the plasma electrophoretic pattern unless the serum is saturated. It may, however, be worth while doing serial electrophoretic examinations.

Because of concomitant secondary coccal infection and the destructive effect of staphylococcal necrotoxin, it is necessary to make full use of antibiotics. Broad spectrum oral antibiotics are preferable to injections of penicillin and streptomycin, provided the organisms are sensitive and the risk of side-effects, particularly diarrhoea, is borne in mind. An adequate supplement of vitamin B complex and ascorbic acid should be given.

Conclusion and Summary

A case of a 6-month-old male infant with vaccinia gangrenosa is described. The local vaccinal reaction progressively enlarged and new lesions continually appeared. Plasma protein studies revealed agammaglobulinaemia. Virological studies confirmed the presence of vaccinia. There was secondary staphylococcal infection.

It would appear that the patient had no humoral defences against the virus, presumably because of the deficiency of gamma globulin and thus the subject was a perfect medium for the cultivation of vaccinia virus, which in consequence produced gross cutaneous and visceral damage. The patient was treated with intramuscular injections of vaccinia gamma globulin and various antibiotics without success. At necropsy the disease was characterized by lymphoid atrophy, absence of healing and poor inflammatory response.

Patients with agammaglobulinaemia should not be vaccinated and patients with generalized vaccinal reactions should be examined for gamma globulin.

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I am particularly grateful to Dr. Norman for his encouragement in the preparation of this report, and Dr. Bodian for the findings at post-mortem examination.

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References

Acland, T. D. and Fisher, C. H. (1893). *Trans. clin. Soc. Lond.*, 26, 114. Cited by Laurance *et al.* (1952).

Apt, L. (1953-54). *Yearb. Pediat.*, p. 67.

Barbero, G. J., Gray, A., Scott, T. F. McNair and Kempe, C. H. (1954). *Amer. J. Dis. Child.*, **88**, 395.
——, ——, ——, —— (1955). *Pediatrics*, **16**, 609.
Bigler, J. A. and Slotkowski, E. L. (1951). *Ibid.*, **7**, 24.
Blank, H. and Rake, G. (1955). *Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man*, p. 110. London.
Dible, J. H. and Gleave, H. H. (1934). *J. Path. Bact.*, **38**, 29.
Dudgeon, J. A. (1956). Personal Communication.
Hall, G. F. M., Cunliffe, A. C. and Dudgeon, J. A. (1953). *J. Path. Bact.*, **66**, 25.
Hutchinson, J. (1879). *Brit. med. J.*, **2**, 960.
Hutchison, J. H. (1955). *Lancet*, **2**, 844.
Keidan, S. E., McCarthy, K. and Haworth, J. C. (1953). *Archives of Disease in Childhood*, **28**, 110.
Kozinn, P. J., Sigel, M. M. and Gorrie, R, (1955). *Pediatrics*, **16**, 600.
Laurance, B., Cunliffe, A. C. and Dudgeon, J. A. (1952). *Archives of Disease in Childhood*, **27**, 482.
Leading Article (1955). *Brit. med. J.*, **2**, 32.
Ministry of Health (1950). Annual Report of the Chief Medical Officer. Pt. II, p. 22. Published 1952.
—— (1951). *Ibid.*, Pt. III, p. 26. Published 1953.
—— (1952). *Ibid.*, Pt. II, p. 32. Published 1953.
—— (1953). *Ibid.*, Pt. II, p. 31. Published 1954.
—— (1954). *Ibid.*, Pt. II, p. 36. Published 1955.
Shortt, C. J. de Vere (1933). *Brit. med. J.*, **1**, 1004.
Stokes, W. (1880). *Dublin J. med. Sci.*, **69**, 497. Cited by Laurance, *et al.* (1952).

A SUGGESTED MEDICAL CLASSIFICATION OF HANDICAPPED CHILDREN

BY

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Considerable attention is being given at the present time to the problems of handicapped children. A session at the Annual Meeting of the British Medical Association (1956) and an entire issue of a medical journal (*Practitioner*, April, 1955) have been devoted to this problem. Every help possible should be given to these children for humanitarian reasons. By helping them to develop to the full such faculties as they possess there should be a reduced demand upon the community when they reach adult life. A recent survey (Carnegie Trust, 1956) showed that the provisions for handicapped children throughout the country were very patchy. A more extensive study of the problem is now being made under the auspices of the Carnegie Trust.

A handicap is a relative condition and its definition is difficult. Children may be considered to be handicapped, if, mentally or physically, they lag behind their contemporaries, or if they require special care, or if they have to make special adjustments in educational, emotional or social spheres. Whatever definition is used there will always be a number of borderline cases.

Handicapped children are usually grouped according to the cause of the handicap. There are those with deficiencies of the special senses, the blind and the deaf; those with locomotor difficulties, the cerebral palsied and the paralysed; those with chronic illness, the cardiac invalids, the asthmatics and the diabetics; those who are emotionally disturbed, and those who are mentally retarded. This method of grouping gives no indication of the child's functional disability. For example, a child labelled 'spastic' may have abnormal reflexes in one limb but no functional disability, whilst another 'spastic' may be immobilized with quadriplegia. Quibell (1956), dealing with severely physically handicapped children, found that the anatomical diagnosis alone was inadequate, and discussed a method of functional assessment suitable for this group. During a current study of the problems of mentally retarded children a classification was devised which indicated functional disability. This classification, somewhat expanded, is presented below as it is thought that its application to all handicapped children might be useful.

Method of Classification

During the last war a comprehensive form of medical assessment known as the Pulheems System was introduced into H.M. Forces (Fletcher, 1949). Using this system it was possible to construct a profile which indicated a person's abilities. Personnel were directed to posts to which they were best fitted, as shown by their profiles. The proposed classification of handicapped children is similar. It allows one to draw a profile of disabilities. The profiles will show the nature of the help needed by the handicapped children and will allow the selection, from a group, of those children who will benefit from any particular form of assistance.

The classification may be known by the initial letters of the sections, P U L H E S T I B : P relates to general physique, U relates to the upper limbs, especially to manipulative ability, L represents locomotion, H hearing and E eyes; S indicates speech whilst T means toilet, I intelligence, and B behaviour.

Each section is divided into four grades. Grade 1 is normal or full ability, and grade 4 complete absence of ability in each section. The addition of the suffix A to the grade indicates that that grade is achieved with the aid of special apparatus. The abilities covered by each grade together with comments upon their significance are shown in Table 1.

The classification in full would apply to children aged 5 years or over. It is important that younger handicapped children should be included. It would probably cause confusion if a young child were given a low grade simply because he was not yet

TABLE 1

'PULHESTIB PROFILES' FOR HANDICAPPED CHILDREN

Section	Grade	Ability	Significance
P (Physique)	1	No deformity No reduction of exercise tolerance Medical supervision not required	This section indicates general physique, exercise tolerance and for children at school, attending centres or in institutions, some indication is given of the need for medical supervision.
	2	Some deformity or reduced exercise tolerance, occasional medical care needed	
	3	Deformity or reduced exercise tolerance or both. Possibly frequent infections. Needs frequent medical care	
	4	Completely disabled. Possibly bed- or chair-ridden	
U (Upper limbs)	1	Able to feed, wash, dress self Can handle pencil and pen	This section indicates the possible need for physiotherapy and in a class the teachers will know the number of children needing help with dressing and feeding.
	2	Assists with feeding, dressing and washing but needs help to complete task	
	3	Needs complete supervision for feeding, washing and dressing	
	4	Arms are useless and cannot hold objects	
L (Locomotion)	1	Able to walk, run, go up and down stairs and climb	This section indicates possible needs for physiotherapy, orthopaedic appliances, special carriages. It may help when the family are advised about housing. It indicates the possible need for conveyance to school.
	2	Can walk and possibly run but needs help to go up and down stairs	
	3	With help can take a few steps or walk a short distance	
	4	Unable to walk even with help	
H (Hearing)	1	Normal hearing	These grades correspond closely to those already in use and recommended by the Board of Education (1938). Their Grade I would be included in 1, their IIa as 2, their IIb as 3 and their Grade III as 4.
	2	Partially deaf: with some help can make satisfactory progress in ordinary school	
	3	Partially deaf; unable to progress in ordinary school	
	4	Severely or totally deaf	
E (Eyes)	1	Normal vision. No strabismus	The grades used here correspond very closely with those formulated by the Ministry of Education (1945). They have similar significance with regard to training.
	2	Partially sighted but with help able to make progress in ordinary school	
	3	Partially sighted and even with help unable to progress in ordinary school	
	4	Blind	
S (Speech)	1	Speaks well; no speech defect, can relate a simple story	This section is closely linked with that of I (Intelligence.) It is included to indicate those children who might be helped by speech therapy, those who may have difficulty conveying their wants and it may possibly indicate the need for investigation of hearing.
	2	Speech of short phrases, possibly with speech defect	
	3	Single words or sounds to indicate wants, possibly speech defect of such severity that understanding is difficult	
	4	No words, meaningless sounds	
T (Toilet)	1	Attends to self, dry at night	This section indicates to teachers the degree of attention to be given to the child. It also allows those children to be selected who cannot be handled at a centre because of defective toilet control. The parents of older children in Grades 3 and 4 may have a lot of expense replacing clothing and bed linen.
	2	Asks for attention, needs some help, may be wet at night	
	3	Accidents with wetting, but control of bowel	
	4	Doubly incontinent	
I (Intelligence)	1	Normal (average) intelligence	Grade 4 corresponds approximately with the classification of idiot at present in use, or of severe subnormality as recommended in the World Health Organization report (1954). In the other grades something can be achieved by training and from the profiles of the children the numbers for whom provision is necessary can be obtained.
	2	Educationally subnormal	
	3	Ineducable but trainable	
	4	Untrainable, complete ament	
B (Behaviour)	1	Normal	Behaviour problems are common in normal children and even more common in those who are handicapped. This section indicates those families where the child and the parents need special help and some indication is given by the grading as to whether this should be at home or elsewhere.
	2	Abnormal, but adjustment possible in home environment	
	3	Abnormal, adjustment not possible in home environment	
	4	Seriously abnormal; needs specialist care	

TABLE 2
ILLUSTRATIVE 'PROFILE'

JOHN S., Orchard Villas. Born July 6, 1951

Date	Age	P	U	L	H	E	S	T	I	B	Examiner	Comments
July, 1955	4 yr.	2	X	X	1	1	2	2	3	2	A. Roe, G.P.	M.D. and hemiplegia
Sept., 1955	4¼ yr.								3	2	B. Shaw, psychiatrist	
Dec., 1955	4½ yr.			Xa							N. Ricks, orthopaedic surgeon	Walking appliance
July, 1956	5 yr.	2	2	2a	1	1	1	2	3	1	A. Roe, G.P.	
Nov., 1956	5½ yr.								2	1	B. Shaw, psychiatrist	

old enough to have acquired those particular abilities. This applies to the section, U, L, T and S. It is suggested that for the child under 5 years of age the sections P, H, E, I and B should be used as indicated. The sections U, L, T and S should be left open until the age of 5 unless the abilities of grade 1 are reached earlier. If there is evidence that retardation in these fields should be expected then a cross is entered in the section.

An alternative form of recording the emotional characteristics may be considered. The most typical feature of the child's behaviour would be indicated: for example, D=destructive, N=noisy, S=sociable.

It is visualized that the parents or guardians of the child would have one copy of the assessment and that another copy would be kept in a central bureau. This central bureau might be organized and financed by the State, by voluntary organizations, or by some completely independent association. The assessment would be initiated by the family doctor.

A method of recording the classification is shown by illustrating the case history of a handicapped child (Table 2). The names and dates in this example have been altered deliberately.

John was examined by his family doctor when he was 4 years old. He was found to be mentally retarded and to have a hemiplegia. Because he had a very sheltered home life he was quiet and timid and had to be placed in grade 2 for his behaviour. Advice about his care was given to the parents. Physiotherapy and a walking appliance were arranged by the orthopaedic specialist. When he was 5 years old, John was re-examined and the full classification was then entered. As a result of an improved parental attitude following advice and John's increased confidence as he became more mobile with his walking appliance, his behaviour improved and he could be raised to B1. The second assessment of intelligence allowed him to be in grade I 2 at least for a trial at an E.S.N. school. When he was ready to start at the E.S.N. school his profile indicated that he would probably require a conveyance to school (L2A), and that the staff should be prepared to assist with feeding, washing and dressing (U2) and with the toilet (T2).

A number of handicapped children seen recently have been classified by this system and the results are shown in Table 3.

Discussion

Many different workers are interested in handicapped children—family doctors, school medical officers, social workers, almoners, physiotherapists, speech therapists, psychologists, teachers in both

TABLE 3
CASES CLASSIFIED BY 'PULHESTIB' SYSTEM

Name	Age	P	U	L	H	E	S	T	I	B	Comments
Lorraine	10	2	2	2	1	1	1	1	1	1	A girl with hemiplegia. She has physiotherapy. Her home has few steps and is very near her school to which she is able to walk. The teachers help her with dressing.
John	8	1	2	1	1	1	2	1	3	1	A boy classed as an imbecile. Whilst S2 may indicate the need for speech therapy, the therapist should realize from I3 that there may be little response. He attends an occupation centre.
Peter	8½	3	2	3	1	1	2	3	3	2	Another imbecile boy of similar age to John. He has a hemiplegia and epilepsy. He cannot walk far and has to be carried up and down stairs. His widowed mother is finding this a great strain. The house is on a hill so he is seldom taken out. He is aggressive. The Local Authority could help by considering rehousing to a flat area and by the provision of a power-driven invalid carriage. The Parents' Association might help by finding someone locally who would go in to take Peter to bed at night and bring him down again in the morning.
Christine	9	2	1	2	1	1	1	1	1	1	A girl with severe asthma and emphysema. The indications are for physiotherapy and either a school near home or a residential school. If the latter P2 indicates the need for occasional medical supervision.

ordinary and special schools, and many others. Some of these, expert in their own spheres, would be helped to appreciate by the profiles of disabilities the other aspects and difficulties of the handicapped child. Because some of these professions are expanding, and some employ a large proportion of women, there will always be a considerable number of young and relatively inexperienced workers. They should find the classification a useful guide.

It is seldom possible in rural areas to have groups of handicapped children such as are seen in cities. Those who work in country areas are likely to see children with a varied assortment of handicaps. Their work should be simplified by a uniform classification applied to all handicapped children.

Children often have multiple handicaps. In an unselected group of 100 ineducable children in Sheffield there were 29 children with other handicaps. It is very easy for attention to be concentrated on one handicap with relative neglect of the other handicaps. In the proposed classification equal prominence is given to each disability. It is hoped that this will lead to the easier management of the child with multiple handicaps.

Ingram (1955), in a report on cerebral palsy, pointed out some of the fallacies of the surveys of handicapped children. The current survey of mentally defective children has confirmed these difficulties. A uniform system of recording handicaps should make surveys easier and more accurate.

The consideration of help for handicapped children requires a consideration of financial aid. It is sometimes said that money given to handicapped children would be better spent on healthy children. This is a hard view, but there never will be unlimited resources. It is necessary, therefore, that the best possible use is made of the funds available. The proposed classification should be helpful by making possible a reasonably accurate estimate of the needs of groups of children. Duplication of work would be avoided. Voluntary contributions should be used for the purpose for which they are given. Certain illnesses, however, have an emotional appeal greater than their relative needs so that their funds are over donated to the detriment of other, less 'popular', illnesses. In an Editor's column (1956) it was pointed out that the amounts raised by some of the 'Funds' (in 1954) showed a total lack of relationship between the relative importance of the disease, as based on the number of victims, and the amounts raised. A classification of handicapped children according to their disabilities rather than their diseases might encourage a more even distribution of donations.

The parents of handicapped children often do not fully understand their child's difficulties and they may receive little guidance for the future. When they know their child's assessment they should appreciate the directions in which their child might be helped. They should never feel that the case had been abandoned as hopeless. The parents of even the most derelict child can be helped by advice about feeding and nursing, by the provision of invalid carriages, by the occasional opportunity of a rest from their burden.

As the children grow older the pattern of their profiles should give a good indication of their capabilities in adult life. Rehabilitation to adult life would be made easier.

This classification is advanced as an attempt to unify the approach to the problems of handicapped children. It may be considered to be Utopian; it may be considered to be impracticable; but some purpose will have been served if it is considered.

Summary

A system of classification of handicapped children is put forward which will give a profile of the children's disabilities. It is hoped that a system such as this will lead to a more uniform approach to handicapped children and will enable the various workers to appreciate all aspects of these children.

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References

Board of Education (1938). Report of the Committee of Inquiry into problems relating to children with defective hearing. H.M.S.O., London.

British Medical Association (1956). Report of Annual Meeting. *Brit. med. J.*, **2**, 222.

Carnegie Trust (1956). Unpublished data.

Editor's Column (1956). *J. Pediat.*, **48**, 822.

Fletcher, R. T. (1949). *Brit. med. J.*, **1**, 83.

Ingram, T. T. S. (1955). *Archives of Disease in Childhood*, **30**, 85.

Ministry of Education (1945). Handicapped Pupils and School Health Service Regulations, No. 1076.

Quibell, E. P. (1956). *Brit. med. J.*, **2**, 991.

World Health Organization (1954). *The Mentally Subnormal Child. Wld Hlth Org. techn. Rep. Ser.*, No. 75.

THE IMPORTANCE OF AUDITORY COMMUNICATION*

BY

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Communication, that is transmission of information to the outside world and receiving information from it, is a vital function of every single living unit.

In the simplest organism the information is also of a simple nature, for example, a chemical reaction, or a tactile sensation. In an organism of higher complexity the information necessary for life will be correspondingly more complicated.

Human beings built for themselves a system of symbols, a language, that helps them to transmit adequately the immense variety of information they require. Sensations of sound were used as the basic material for building this language. That is the chief reason why hearing, in other words ' auditory communication', is of supreme importance to man.

It was not by accident that, when it was necessary to communicate information of great complexity with great speed and economy, sound was used as the most suitable medium available. There were good physical and physiological reasons for it.

The physical reason is the vibratory aspect of sound in air and in the basilar membrane of the inner ear. Frequencies of vibration from 100 to 10,000 cycles per second give a tremendous number of possible combinations. The human ear can distinguish about 340,000 sounds of a certain pitch and loudness. These can be transmitted with speed and little effort. Above all, frequency analysis is that outstanding characteristic of the auditory apparatus which enables us to encode the great variety of information in this type of communication. Other sensations also involve analysis on a frequency basis but only in hearing is it the fundamental operation upon which everything else is overlaid.

The vibratory (physical) aspect of sound is, however, only part of what makes up the complex sensations resulting from it. This becomes clear when the most important of all sounds are considered—that is speech.

The acoustic wave forms of speech can be measured and analysed in great detail. Various elements of the complex wave form can be studied, and it can be determined which of these elements are most vital for the transmission of the information. It is possible to reduce the highly complex wave form of speech to an infinitely clipped version, yet the speech remains intelligible (Licklider, 1950), and the critical information of the message is still transmitted adequately. It means that the information-bearing elements of speech sound can be, so to say, extracted from the complex acoustic wave form of natural speech. In other words, natural speech has a great redundancy. The brain is adapted to exploit this great redundancy of natural speech to maintain communication under adverse conditions, which usually occur in the form of ever-present surrounding noise. This is one of the important reasons why this type of communication is so efficient, and one of the biophysical reasons for the efficiency and superiority of auditory communication by speech.

We must mention another important reason. Communication of language means transmission of thoughts from brain to brain. Each thought may be broken down into images. Each image corresponds to one word and to one individual visual picture. According to the experimental phoneticians each spoken word may be broken down—on the average—into four elementary sounds, called phonetic elements or phonemes (Dreyfus-Graf, 1950). Western European languages allow for articulation, on the average, of a maximum of 12 such phonetic elements per second. It means that three words can be communicated from brain to brain per second. Individual perception of pictures begins to become confused when the speed exceeds more than three words. This is nearly the speed of thinking. The rhythm of 12 elementary sounds (phonemes) per second allows the spoken language to follow nearly the speed of thinking. Auditory communication is then the best available, most efficient and economic method of communicating language from brain to brain. It has taken a

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long time for mankind to develop it. The primary function of the larynx, phylogenetically, is not to produce sound, but to prevent foreign bodies from entering the respiratory tract. Production of speech sounds, and consequently oral language, is, so to say, an artificial addition. It must have taken long in the history of man to develop the fine neuromuscular coordination necessary for the voluntary movements which produce speech sounds, and hearing is the most important feedback control of this neuromuscular mechanism. If hearing is absent from birth or early childhood, and if a child remains untaught, from many aspects he stops at a stage of development comparable to that of the earliest pre-historic stage of man.

If we do not want to leave such a child stuck at that primitive stage, we must give him a language, and preferably teach him in such a way that he should be able to communicate that language orally, by speech. But not only because this is the most efficient method of communication. There is an additional and most important reason. We know that we cannot make out of a profoundly deaf individual a normal person. Our aim should be to make him into a person who is able to communicate in the normal hearing society with a reasonable degree of efficiency, and is reasonably adjusted to his disability without segregating him for ever. It means that we must help him to achieve independence in communication in the hearing society. And the greatest degree of independence in communication in a hearing society is communication orally, by speech.

It is almost a truism to say that early detection of impaired hearing will influence greatly the success of rehabilitation as defined above. Early detection of deafness is of prime importance for several reasons. If the deaf child is to be expected to communicate with reasonable success in a hearing society, he needs to be exposed to a normal speech pattern. This exposure produces the maximum results when it is begun as early as possible in the child's life (Fry and Whetnall, 1954).

Another reason for early detection is the following one: Apparently some important language patterns are set during the early years and probably much of it before the child enters school. Further training exerts only a modifying influence. It is necessary to fix these patterns for the deaf child as early as possible, and before he starts his schooling. Still another reason is the enormity of the task for a deaf person to achieve independence in communication in a hearing society. To illustrate the difficulty I will borrow an analogy from information theory.

Natural speech is transmitted over a communication channel of full capacity. As I mentioned previously much of this capacity is redundant. Shannon in his communication theory has shown that perfect transmission is possible over a channel of minimum capacity, admitting no redundancy at all. The price is an elaborate terminal coding equipment. The same happens in communication of a profoundly deaf person. For him, when receiving a signal, the rule of all or nothing applies. He has to communicate over a channel of minimum capacity, without any redundancy, and our task is to provide him with a terminal coding equipment, that is, we must teach him the correct interpretation of the signals which come to him over a communication channel of minimum capacity, admitting no redundancy.

Early Detection of Deafness

What are the chances of early detection of deafness? Naturally, it is easier to detect an almost total or very severe loss of hearing than a partial, less severe one. This is recognized by most people, but the signs, symptoms and serious consequences of partial deafness are less well known, although numerically these cases are more important.

A very severely deaf child will not react to everyday sounds at all; his speech will not start to develop; it will be soon noticed that there is something wrong. It may occur to the parents that the child is deaf.

On the other hand, a child with, let us say, considerable amount of hearing for lower notes but severe impairment for the higher ones, will react to a variety of everyday sounds and he will start to speak; in familiar circumstances he may hear and understand many words and sentences (possibly with the help of spontaneously acquired lip-reading). But when he has to learn a great number of new words and hear them in unfamiliar circumstances he will fail and show various disorders. It may not occur to the parents, or even to various educational, psychological and medical specialists that the trouble is a serious hearing loss. This suggestion may be encountered with scepticism. The child obviously can hear, therefore he cannot be deaf.

The term 'deafness' is misleading. Usually it is associated with the profound hearing loss which used to be labelled by the now obsolete term 'deaf and dumb'. The type of partial deafness, however, which I described, is very much more frequent. Its serious symptoms are not always recognized.

Let us consider how language development is influenced in the deaf child.

A normal child first develops some awareness of happenings; he learns a few everyday situations and

the meaning of his experiences. It takes him eight or nine months to gain this inner language before he begins to use receptive language, that is before he begins to understand a few words spoken by others (Myklebust, 1954). It takes him another four or five months before he begins to use expressive language and speak his first words. No child can learn to speak unless he has learned to understand some of what is said to him. The child understands a limited vocabulary before he is able to use it as a means of oral expression (Pratt, 1950).

This process of developing language in three steps, inner, receptive, and finally expressive language, will be modified in the deaf child according to the type of his hearing loss. First let us consider some of the symptoms in a profoundly deaf child. The profoundly deaf child will not reach the second stage of language development, that is, receptive language. For months nothing abnormal may be noticed. Some parents may observe at a very early age, 4 to 5 months, that the child does not respond to sounds, but frequently the first symptom which arouses suspicion is lack of speech development. The child produced babbling noises in early infancy but he did not form any definite speech sounds at the appropriate time. Later, when the child has a desire to communicate something to his parents but is not able to do so, signs of frustration appear. It may assume forms of tantrum or violence. He may try to communicate more frequently and forcibly by crying or gesticulation. When the stage of babbling has passed, the child may not use his voice any more, and will gesticulate more frequently.

Some other signs suggestive of deafness in infants are response to some noises as opposed to voice; augmented visual vigilance and attentiveness; alertness to gesture and movements; yelling, screeching to express pleasure, annoyance or need.

Often it is reported that such a child is terrified in the dark. A normal child, when put to bed, and the lights are switched off, hears a variety of ambient sounds. Ambient noises surrounding us day and night are full of meaning, and many have a significant emotional value. A normal child does not usually feel cut off from the outside world in the dark. A deaf child is plunged into complete isolation and loneliness.

These symptoms are not unusual in other categories of children and may have different causes. The important thing is, that when causes are considered, deafness should be at the top of the list. Often it is not on the list at all.

If a child does not speak within reasonable limits of the normal age, it should be always considered that his hearing is impaired, unless proved otherwise by appropriate testing.

The picture will be different in the child with severe partial deafness. He may arrive at the stage of receptive language but somewhat later than the normal age. He hears a variety of speech sounds, and initially he attaches the correct meaning to some words, but later, when his activities involve him in new situations and he is presented with a greater variety of words, his difficulties gradually increase.

The following will explain the causes of some of the difficulties a partial deaf child has to face:

Normally, acoustic wave forms of different shapes are responsible for significant variations of auditory sensations. They form different patterns of excitation in the appropriate centres of the central nervous system. In the case of the deaf individual, acoustic wave forms of different shapes may produce identical or similar sensations, and discrimination may be very difficult. Different words may sound much the same to the child, but it seems to him that his parents attach on occasions different meanings to what to him sounds the same, *e.g.*, the words 'bottle' and 'water' may sound something like 'o-a' on both occasions. But at one time his mother will present him with a bottle, and on another occasion she will point to water in the bath. Still later, when the child will try to use expressive language, and will ask for one thing, saying something like 'o-a', and meaning water, but will be presented with a thing (that is 'bottle') which he did not want, he will get frustrated, angry and confused.

I have no space to describe this process in detail, and how it is modified according to the various types of hearing loss in the partially deaf child. I can only summarize some of the consequences.

Language development will be retarded, a speech defect will develop, usually an articulation defect (some consonants will be missing, mispronounced or confused with others), the voice may have good intonation (in the almost totally deaf child taught to speak, intonation is lacking, and the voice is monotonous and flat). The child will watch intently the speaker's face, and may acquire a fair amount of lip-reading which will enable him to understand much of speech in tête-à-tête conversation (in some intelligent children surprisingly well). In unfavourable circumstances they may not hear or may not understand what is said. Frequently they are accused of not listening, being inattentive, lazy, and are punished for it. In fact, because of the limitations of their communicating ability, their power of attention to speech is affected. Attention is a function which selects, out of a total mass of incoming signals those which have certain character-

istics, and so doing avoids overloading the mechanism which carried out the final analysis of speech (Broadbent, 1954). A deaf person, communicating through a channel of limited capacity for which the rule of all or nothing applies, cannot rely on a selection from a mass of incoming signals automatically—he must pay attention all the time—and he soon tires. Finally he cannot pay attention at all. At school he remains backward. He may not be able to localize the source of various sounds, and often is puzzled by this, or he may not be able to determine what made what type of sound.

In another case, speech may be unintelligible. The child may use a jargon, perhaps intelligible to his mother but to nobody else. Because of inability to communicate, extreme degrees of frustration may appear, and he also will try to communicate increasingly by crying, shouting and gesticulation. Some will gradually give up listening even to what they can hear, because it does not mean much to them or confuses them. They withdraw into a silent world because a hearing one causes them only trouble. On this account they may be assessed as totally deaf, and sent away to a residential deaf school, in spite of the fact that, with early detection of the true type and degree of their hearing loss and adequate auditory training, they could make satisfactory progress in a normal school and live a normal home life. They may be misdiagnosed altogether and declared mentally defective. The differential diagnosis between mental deficiency, or low mental capacity and deafness is the most important one. No child should be declared mentally deficient without making certain that his hearing is normal.

In summary we can say that the early detection of partial deafness on the whole is much more difficult than the severe, almost total hearing loss. This is important when it is realized that numerically this partially deaf group is larger. The defect may become obvious to a lay person comparatively late. Even to certain specialists the significant symptoms and serious consequences of this type of deafness are comparatively unknown.

What are then, under present conditions, the chances of early detection and correct diagnosis of deafness? Theoretically there are three, so to say, lines of defence: (1) Screening all children without exception; (2) screening those in whose history there is a possible cause of deafness; (3) observation and testing children with a definite symptom known to be associated with deafness.

(1) The first case, that is routine testing of all children at an early age, is not practicable as yet. Screening of schoolchildren soon after their entry to infant school is carried out, as a routine, in many counties. About 1% to 2% of these are found with some degrees of significant hearing loss. Some of these have a serious hearing loss, and at this stage already much valuable time has been lost, and frequently much harm has already occurred.

A satisfactory screening test for infants has not been worked out yet. They can be tested, but this needs a special set-up and experience.

Attempts are made in some places to train health visitors and teach them to apply simple tests, but on the whole it is not satisfactory. There is always a danger that the severe or moderately partially deaf child will be missed. One of the contributions health visitors can make is education of the public. When they visit homes, they can draw the attention of mothers to the possibility of deafness.

The knowledge of the public in these matters is surprisingly limited. Authors of numerous books, meaning to give various types of advice to parents of young children, show complete ignorance of this problem almost without exception.

We must admit that there is no satisfactory screening test available for the early detection of these types of hearing loss. There is a positive danger in applying crude screening tests at this stage. Partial deafness may not be recognized. When its effects become apparent at a later stage of development, the fact that the child has been previously labelled (as a result of a crude screening test) as of 'normal hearing', or 'not deaf', may lead to the alternative diagnosis, that is mental backwardness. The child may remain labelled as such for a long time before the true nature of his troubles is disclosed.

(2) Screening of children with a known possible cause of deafness in their history is a more practicable approach. If there is a definite history of some of the causes of deafness, one should not wait till pronounced symptoms appear. This is considered, and with some justification, an ideal which cannot be achieved in practice. Still, it could be achieved provided the cooperation of everyone concerned with the welfare of the child would be forthcoming, and I would include the obstetrician, the paediatrician and the medical officer of health.

If there is a history of deafness in the family; if a child's mother had rubella or any other virus disease during a critical stage of pregnancy; if the child suffered from anoxia at birth, or from asphyxia in a premature child, or the labour was unusually protracted, and the delivery was complicated; if the child had haemolytic disease of the newborn or was jaundiced as a result of premature birth or had kernikterus, in all these cases the offspring should be tested without exception at an appropriate time.

This approach has great possibilities from the practical point of view of detection, and also it would add significantly to our knowledge of the incidence and pathology of certain types of deafness. Studies have been, so far, almost exclusively retrospective. The above approach would provide us with valuable prospective types of investigation.

(3) The third type of approach, the one practised, is testing children with a symptom or sign known to be associated with deafness. Lack of speech; retarded language development; speech defect; sigmatism (that is, mispronunciation of 's' or any similar confusion of speech sounds in a similar range of frequency); lack of speech comprehension; serious emotional frustration combined with various degrees and types of speech defect; general backwardness at school; those who suffer from a condition known to be associated frequently with a hearing ing loss, such as paralysis of cerebral origin; post-meningitic and post-encephalitic conditions; history of fractured skull or severe head injury; cleft palate, and of course various types of middle-ear disease. But even this approach is not as yet fool-proof. For example, not all children with cerebral palsy have their hearing tested, and not all who had a cleft palate, a speech defect, or those who survived after cerebrospinal or tuberculous meningitis. They all should have, without exception, their hearing fully tested.

I must mention now a few principles concerning hearing tests:

(1) There is no single form of testing which will give a complete picture of the total hearing capacity of an individual.

(2) One should not draw any far-reaching conclusions or make final decisions on the basis of observations carried out on one single occasion.

(3) Hearing tests are subjective tests requiring cooperation. There is no mechanical device which would enable us to test a child without gaining his confidence or cooperation. The handling of the child is decisive.

(4) A test should be of such a nature that it should not be associated with unpleasant or frightening experiences. A procedure which is associated with such experiences is, from our point of view, no procedure at all. The child's cooperation will be required in increasing degrees for future testing and rehabilitation. Destroying it at the very beginning in any way defeats the purpose of his attendance for examination.

(5) The child's obvious reaction to certain sounds or his understanding of familiar speech sounds in tête-à-tête conversation does not mean that the child could not have a hearing loss. When deafness is suspected, only a complete test is conclusive. The all or nothing rule applies to hearing tests, *e.g.*, when hearing for pure tones is tested, we obviously do not test only for isolated frequencies in a haphazard manner. When hearing for speech is tested, a haphazard collection of words or sentences cannot give a conclusive result. A list of phonetically balanced words and sentences must be used and acoustic conditions of the room must be considered.

There is a variety of testing methods available: Observation of reactions to percussion instruments, to speech sounds, or pure tones; audiometric tests for pure tones; live voice tests consisting of phonetically balanced, specially selected, word and sentence lists. The child can be observed in a play situation or conditioned to perform certain simple actions to a definite sound stimulus. With infants, instructions can be given to the parents how to condition a child to certain sounds at home, or how observations should be carried out and recorded over a period of time.

At a very young age we can always give a reliable answer at least to the following questions; Is this child totally deaf? Is he severely deaf? Is he moderately deaf? Is his hearing within normal limits? This is enough for the necessary urgent measures to be taken for treatment, if this is indicated. Gradually one can obtain more information, and within a reasonable time one can get a complete picture about the child's capacity to hear and measure his hearing loss exactly.

When the effect of the hearing loss on a child and prognosis is considered, one should not do so on the basis of the hearing loss alone. A careful study of the learning ability is of greatest importance. Mental ability, personality, and emotional condition of the individual modify the hearing disability. On the other hand the hearing disability, which affects a growing organism, will influence the intellectual and emotional development of the child. In fact it is essential to consider the child as a whole.

Associated symptoms may necessitate a modification of testing procedures, and also they can be an important guide in our search for possible causes and pathology of deafness. For example, a slight muscular incoordination, which might have been overlooked because it did not cause a marked disability, may disclose the cause and pathology of deafness in that child, that is kernikterus. Similarly physical examination may disclose, for example, an abnormally wide nasal bridge, combined with a deformity of the inner angle of the eyelids (epicanthal fold, occasionally combined with different coloured eyes, or a white forelock) and so disclose the special type of hereditary deafness associated with these signs.

This points to what I said previously, and even at the cost of repetition I want to emphasize again, namely, that it is important to study not an isolated symptom, but the individual as a whole. It cannot be otherwise with a symptom like deafness, which is basically a communication disorder and has such a profound influence on the whole person. This also indicates another important necessity: the study of the individual as a whole can be carried out only by a clinician. That is the reason why I would emphatically say that the answers to the fundamental problems of deafness will not be given by technicians but by clinicians. Obviously this work cannot be done by an individual or a single speciality. It requires the work of a team. Individuals interested in special aspects of deafness joined to form such teams, and this was the foundation of audiology. The otologist, teacher of the deaf, physicist, audiology technician, experimental phonetician, educational psychologist, school medical officer, are part of such a team. I think, however, that representatives of some other specialities are still missing, and one of the most important members of an audiology team should be a paediatrician.

I will end by quoting the words of an eminent worker in the sphere of child health, Gesell (1956), who said:

> 'It is not normal to be deaf, but the deaf can be remarkably normal as individual personalities if we guide them into the right methods of managing their handicap. Our aim should not be to convert the deaf child into a somewhat fictitious version of a normal hearing child, but into a well adjusted, non-hearing child, who is completely managing the limitations of his sensory defect.'

References

Broadbent, D. E. (1954). *Attention and Memory in Listening to Speech.* (Paper for symposium on speech, Acoustics Group, Physical Soc., London.)

Dreyfus-Graf, J. (1950). *J. acoust. Soc. Amer.*, **22**, 731.

Fry, D. B. and Whetnall, E. (1954). *Lancet*, **1**, 583.

Gesell, A. (1956). *Volta Rev.*, **58**, 117.

Licklider, J. C. R. (1950). *J. acoust. Soc. Amer.*, **22**, 820.

Myklebust, H. R. (1954). *Auditory Disorders in Children.* New York.

Pratt, K. C. (1950). 'Child Development—Early Infancy.' In Monroe, W. S., *Encyclopedia of Educational Research*, rev. ed. New York.

FAILURE OF HYPERIMMUNE GAMMA GLOBULIN TO PREVENT WHOOPING COUGH

BY

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Whooping cough is still a major hazard of infancy. Immunization against it is increasingly practised, but is seldom begun before the sixth month, leaving the infant unprotected in the potentially dangerous first few months of life. It was with these facts in mind that we decided to investigate the effects of hyperimmune gamma globulin in the prevention of whooping cough.

Previous workers (McGuinness, Armstrong and Felton, 1944) had shown that large doses of hyperimmune serum were apparently effective in the prevention and treatment of pertussis and suggested that gamma globulin might be found more effective. Cruickshank (1949) reported that, in controlled trials in three residential nurseries, antiserum prepared in rabbits and horses temporarily protected most children inoculated in the incubation period. We present here the results of two controlled trials designed to evaluate two preparations of gamma globulin made from the blood of hyperimmunized donors in the protection of susceptible home contacts of whooping cough.

Preparations under Trial

In the first trial a special hyperimmune gamma globulin prepared by Cutter Laboratories, California, was matched against an inactive control inoculation. The Cutter product was described by the manufacturers as a refined globulin fraction from the blood of adults having a history of pertussis in childhood, hyperimmunized with Cutter phase 1 pertussis vaccine. The control inoculation was a 1·5% solution of autoclaved gelatin similar in appearance to the globulin solution and put up in identical ampoules. A 2·5 ml. dose of both preparations was used. Each 2·5 ml. dose of the globulin solution contained approximately 200 mg. of globulin obtained from about 25 ml. of human serum.

In the second trial gamma globulin prepared by Dr. M. E. Mackay at the Medical Research Council Blood Products Research Unit, Lister Institute, from the blood of hyperimmunized volunteer medical students was compared with gamma globulin prepared at the Lister Institute from the blood of normal adult donors. A 6 ml. dose of both preparations was used, each dose containing approximately 500 mg. of gamma globulin obtained from about 80 ml. of human serum. Both preparations were in similar containers. The medical students had been inoculated four times at monthly intervals with a pertussis vaccine made by the Michigan Department of Health, which was used as a reference vaccine in a recent Medical Research Council field trial and which was shown to protect children (Report, 1956). Some of the students had severe reactions, particularly after the second inoculation, and could not complete the course.

In both trials the preparations bore labels of identical appearance inscribed with a number from a random series to indicate the order in which they were to be used.

Laboratory Tests

Both hyperimmune gamma globulins were examined by Dr. Naomi Datta of the Standards Laboratory, Colindale, and Mr. A. F. B. Standfast of the Lister Institute. Dr. Datta tested the preparations during and after the clinical trials and reported *Haemophilus pertussis* agglutination titres of 1/1024 for Lister and Cutter products on each occasion. This may be compared with the following titres for eight batches of normal Lister gamma globulin taken at random: 1/32, 1/64, 1/128 (four batches) and 1/256 (two batches). Mr. Standfast, using the intracerebral mouse test (Report, 1956), examined

* In receipt of a research grant from the North Eastern Metropolitan Regional Hospital Board.

the Lister hyperimmune gamma globulin, the plasma pool from which it was prepared and some hyperimmune rabbit serum before the clinical trials in 1953. He tested the Cutter hyperimmune gamma globulin, and these sera again, after the trials in 1956. He concluded from his results that the Lister gamma globulin was about twice as potent as the original plasma; that the Cutter and Lister products and the rabbit serum were of approximately equal potency; and that the Lister gamma globulin maintained its strength between 1953 and 1956.

Method of Trial

Healthy children under 5 years of age who had been in contact with other children with whooping cough in the same household were eligible for treatment provided they were symptomless, had no past history of the disease and had not been actively immunized against it. General practitioners and medical officers of health in certain London boroughs were asked to help in finding contacts meeting these requirements. Doctors were asked to inform us, if possible by telephone, of suitable families; these were visited without delay. The nature of the investigation was explained to parents and with their permission suitable contacts were inoculated. In the first trial the dose (2·5 ml.) was given within 14 days after the onset of symptoms in the primary case. In the second trial the larger dose (6 ml.) was given within 10 days after the onset in the primary case.

Inoculated children were observed for 28 days to find out if they developed whooping cough. Any child who developed a cough during this period was observed until his symptoms disappeared to determine the diagnosis, the duration and the severity of the attack. An attempt was made to take at least three pernasal swabs from every primary (infecting) case and from every treated contact who developed a cough. The swabs were taken at approximately three to four-day intervals as soon as possible after the onset of symptoms and sent at once either to the Central Public Health Laboratory, Colindale, or to the laboratory of the Queen Elizabeth Hospital for Children, London, where they were examined for the presence of *Haemophilus pertussis*. At the first follow-up visit, usually within 72 hours, a note was made of any inoculation reaction. No untoward reaction occurred in any of the children inoculated.

Details of the primary case and the contact child, together with the serial number of treatment given, the results of the follow-up and of the bacteriological findings were entered on a special record card for each family.

Results

The first trial ran from March to December, 1954. During this time 33 children were inoculated, 17 with hyperimmune gamma globulin (Cutter) and 16 with the control gelatin. In the treated group 10 developed a cough within 28 days and seven of these were classed as cases of moderate or severe whooping cough. In the control group seven developed a cough and four of these were thought to have moderate or severe whooping cough. When only those families were considered in which *Haemophilus pertussis* was isolated from either the infecting child or the contact it was found that seven out of 11 who received the hyperimmune gamma globulin developed moderate or severe whooping cough compared with four out of seven in the control group. As these figures did not suggest that the hyperimmune gamma globulin was having any protective effect it was decided to change to different preparations in larger dosage and to more stringent time requirements.

In the second trial, which ran from January to December, 1955, only 17 children were treated, eight with hyperimmune gamma globulin (Lister) and nine with normal gamma globulin (Lister). Six of the eight and six of the nine developed a cough within 28 days. Five of those who had received the hyperimmune product were ranked as moderate or severe whooping cough and four of the other group were similarly assessed. *Haemophilus pertussis* was isolated in seven families given the hyperimmune gamma globulin and six families given normal gamma globulin. All the contacts that developed moderate or severe whooping cough were in these families. The total number of contacts treated in the second trial was admittedly small, but as suitable contacts were difficult to find and as there was no suggestion that the results were any better than in the first trial, it was decided to discontinue the investigation. The results of both trials are set out in the Table.

Discussion

Gamma globulin prepared from pooled adult serum or plasma has been shown to give passive protection against measles, infective hepatitis and poliomyelitis; the evidence for prophylaxis against rubella is less certain. In mumps and chickenpox reports suggest that this type of gamma globulin is ineffective. The findings of McGuinness *et al.* (1944) suggested that whooping cough contacts could be passively protected with hyperimmune serum. It was hoped that gamma globulin prepared from hyperimmune serum might also prove effective, but our findings do not confirm this.

TABLE 1

RESULT OF TWO CONTROLLED TRIALS OF HYPERIMMUNE GAMMA GLOBULIN IN PREVENTION OF WHOOPING COUGH IN FAMILY CONTACTS UNDER 5 YEARS OF AGE

Trial	Treatment	Bacteriological Evidence of Whooping Cough in Family	No. Inoculated	No. Developing Cough Within 28 Days of Inoculation	No. with Moderate or Severe Whooping Cough
I	Hyperimmune gamma globulin (Cutter)	+	11	9	7
		−	6	1	0
		total	17	10	7
(Dose 2·5 ml.)	Control	+	7	5	4
		−	9	2	0
		total	16	7	4
II	Hyperimmune gamma globulin (Lister)	+	7	6	5
		−	1	0	0
		total	8	6	5
(Dose 6 ml.)	Normal gamma globulin (Lister)	+	6	5	4
		−	3	1	0
		total	9	6	4
I and II Combined	Hyperimmune gamma globulin	+	18	15	12
		−	7	1	0
		total	25	16	12
	Normal gamma globulin or control	+	13	10	8
		−	12	3	0
		total	25	13	8

As the dosage used in the first trial might have been too small it was doubled in the second, but no better results were obtained either in the prevention or in attenuation of the disease. It is possible that a still larger dose might give protection. In the first trial all inoculations were given within 14 days of onset of illness in the primary infecting case but in only seven out of 33 was the interval less than one week. In the second trial all 17 were injected within 10 days of onset but only five were in the first week. Thus in spite of every effort most inoculations were given late in the incubation period. This factor may have contributed to the unsuccessful result but in practice it seems unlikely that contacts could be inoculated much earlier.

Although both hyperimmune gamma globulins contained agglutinating antibody in high titre it does not follow that the factor responsible for protection was also present. Hink and Johnson (1950) showed that in mouse tests the protective antibody was located almost entirely in the γ_2-globulin fraction but only a minor portion of pertussis agglutinins could be recovered from this fraction. Both the Cutter product prepared by Cohn's method and the Lister product prepared by the method of Kekwick and Mackay (1954) consist mainly of γ_2-globulin and would therefore be expected to contain the protective antibodies for the mouse and this was confirmed in laboratory experiments. The intracerebral mouse test has shown some correlation with field trial results of pertussis vaccine (Report, 1956) but it may not be equally useful in the evaluation of sera used for passive immunization. However, even an effective passive immunizing agent could not be expected to protect unless given in time and in sufficient dosage. Nevertheless, our results suggest that hyperimmune gamma globulin in the doses used has at present no value in the prevention of whooping cough.

The management of susceptible children exposed to whooping cough remains a serious problem. Active immunization may be effective even when given as early as 3 months of age (Butler, 1954). Isolation of children suspected to be suffering from whooping cough is still all important, but, should the child in contact with whooping cough develop symptoms, then chloramphenicol or chlortetracycline may reduce the severity and the frequency of the paroxysms (Reports, 1953; Morris and Cockburn, 1954). As these drugs are not without danger suitable children should be carefully selected.

Summary

In two controlled trials 50 family contacts of whooping cough aged less than 5 years were injected with either gamma globulin prepared from the blood of donors hyperimmunized with a pertussis vaccine or with normal gamma globulin or an inactive inoculum (autoclaved gelatin). No evidence was found that hyperimmune gamma globulin reduced either the attack rate or the severity of whooping cough in the contacts.

We should like to thank the following for help in this investigation: Cutter Laboratories and Dr. M. E. Mackay, of the Lister Institute, for supplying the trial preparations, Professor R. Cruickshank and volunteer

students of St. Mary's Hospital, London, for hyperimmune plasma, Dr. Naomi Datta, Dr. H. D. Holt, Dr. B. Levin and Mr. A. F. B. Standfast for laboratory work, general practitioners and medical officers of health who told us of whooping cough contacts, and Dr. W. Cl[illegible]s. Cockburn for advice and help.

References

Butler, [illegible]. R. (1954). *Proc. roy. Soc. Med.*, **47**, 357.

Cruicks[illegible]ank, R. (1949). Fourth International Congress for Micro[illegible]ology, Copenhagen, July 20-26, 1947. Report of Proceed[illegible]gs. Copenhagen, Rosenkilde and Bagger. p. 184.

Hink, J. H. Jr. and Johnson, F. F. (1950). *J. Immunol.*, **64**, 39.

Kekwick, R. A. and Mackay, M. E. (1954). *Spec. Rep. med. Res. Coun.* (*Lond.*), No. 286.

McGuinness, A. C., Armstrong, J. G. and Felton, H. M. (1944). *J. Pediat.*, **24**, 249.

Morris, [illegible]. and Cockburn, W. C. (1954). *Lancet*, **2**, 724.

Report (1953) by the Whooping-Cough Subcommittee of the Antibiotics Clinical Trials. (Non-Tuberculous Conditions) Committee of the Medical Research Council. *Lancet*, **1**, 1109.

Report (1956) to the Whooping-Cough Immunization Committee of the Medical Research Council and to the medical officers of health for Cardiff, Leeds, Leyton, Manchester, Middlesex, Oxford, Poole, Tottenham, Walthamstow and Wembley. *Brit. med. J.*, **2**, 454.

MALIGNANT HYPERTENSION DUE TO PHAEOCHROMOCYTOMA IN A CHILD

BY

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(RECEIVED FOR PUBLICATION DECEMBER 17, 1956)

The case reports of phaeochromocytoma in children have recently been reviewed by Smid and DuShane (1955) who were able to collect details of 32 cases. Since their account further instances have been published by Robinson and Williams (1956) and Mégevand and Ferrier (1954). A further successful case is reported here. Including the present patient, 36 children have been affected; of these, 26 have been subjected to surgery and 18 have survived.

Case Report

The patient was 11 years old when first seen in the Out-patient Department. His mother said that he had enjoyed good health until the age of 8 when he seemed to have stopped growing and was gradually overtaken in height and weight by a younger brother. At the same age the patient began to sweat excessively. Initially the attacks were intermittent and more severe at night, but in more recent months he seemed to perspire to some degree almost continuously. For 12 months he had been unable to play games because of exertional dyspnoea and for four months before admission had complained of occasional frontal headache and vomiting. His vision was not affected. He was admitted to the General Infirmary at Leeds for further investigation on December 13, 1955.

On examination he was small for his age but normally proportioned (height 49 in. and weight 60 lb.). His face was pale and he had an anxious expression. Both hands were red and swollen due to a firm non-pitting oedema which extended as far as the wrists. There was no desquamation of the skin but the general appearance strongly resembled that seen in pink disease in infants. The feet were not so affected. The blood pressure varied from 240/130 mm. of mercury to 280/160 mm. of mercury. All peripheral pulses were present and equal. The resting pulse rate was 100 per minute. Neither changes in posture nor loin massage had any effect on the blood pressure. The heart was not enlarged. The cardiac impulse was forceful and the aortic second sound accentuated. A few fine rales were present at both lung bases. There was no evidence of congestive heart failure. Examination of the fundi revealed bilateral papilloedema with numerous linear haemorrhages and soft exudates. No abdominal tumour was palpable. The urine occasionally contained a trace of albumin. There was no glycosuria.

A blood count gave: R.B.C. 5·2 m., Hb 106%, W.B.C. 15,800 with a normal differential. The fasting blood sugar was 120 mg. %. A mid-stream specimen of urine was sterile on culture and no cells or casts were seen. The blood urea nitrogen was 16 mg. %. The urea clearance test was within normal limits. The serum sodium, potassium, chloride, CO_2-combining power were all within normal limits. The chest radiographs showed a heart of normal size and the lung fields were clear. An intravenous pyelogram showed that both kidneys concentrated the dye well and the calyceal pattern was normal.

For perirenal air insufflation (Dr. D. A. W. Cowie) approximately 400 ml. of air was used, and tomographs were made. On the left a good outline was secured and no abnormal mass of adrenal tissue could be seen. On the right side there did appear to be a larger suprarenal opacity.

An E.C.G. showed some ST segment depression in leads V5, V6, but was otherwise within normal limits.

An assay of the urinary excretion of catechol amines was done at University College Hospital. The pre-operative 24-hour specimen of 1,000 ml. contained approximately 1μg. noradrenaline per ml. and was indicative of phaeochromocytoma. (The output of noradrenaline in normal adult urine is less than 63 μg./24 hours (von Euler, 1954). In essential hypertension the daily excretion of pressor amines is usually less than 100 μg. but occasionally as much as 200 μg./24 hours (von Euler, 1952). Most patients with phaeochromocytoma excrete more than 250 μg. of pressor amines daily.)

Rogitine (phentolamine), 1·5 mg. given intravenously, reduced the blood pressure from 210/150 to 135/110 mm.Hg (Fig. 1).

On January 1, after a hypertensive crisis, the boy developed a minimal left hemiparesis. Any further pre-operative studies were therefore abandoned. For 48 hours before operation he was given 'rogitine' intramuscularly in doses of 1·5 mg. at intervals dictated by the blood pressure responses. On January 4, by an

intrathoracic approach and removal of the tenth rib: Mr. I. Shuckmsith removed the right adrenal gland, This incorporated a firm tumour 4·5 cm. in diameter. The pathological report on the tumour was as follows.

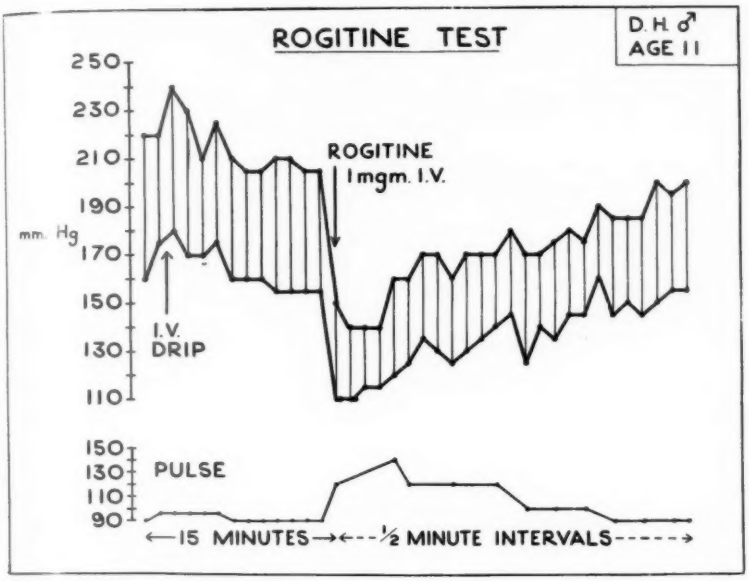

FIG. 1.

'The specimen is an adrenal gland distorted by an ovoid solid circumscribed tumour 4 × 3·5 × 3 cm. with a purple brown cut surface. The tumour appears to be growing outwards from the interior of the gland stretching and thinning the cortex which overlies it. After photography part of the tumour was refixed in bichromate and developed a brownish colour.

The tumour is composed of sheets of syncytial masses of pleomorphic cells. Many have round vesicular nuclei and vesicular cytoplasm resembling cells of the cortex. Others have extremely large deeply basophilic reticular nuclei and no recognizable cytoplasmic boundary. Thin-walled, dilated blood vessels are a feature and there are areas of haemorrhage and degeneration. Sections of bichromate-fixed material show numerous brown chromaffin granules in many of the cells. This is a typical phaeochromocytoma; nothing in the appearance suggests malignant change (Dr. I. Dawson).'

During the induction of anaesthesia, and until the tumour was excised, the blood pressure was controlled by intermittent intravenous 'rogitine' (phentolamine) in accordance with the technique outlined by Helps, Robinson and Ross (1955). After the removal of the tumour the blood pressure was maintained by intravenous noradrenaline and a satisfactory pressure response obtained at a dose of 25 μg. per minute. This concentration was gradually reduced and the infusion discontinued seven hours post-operatively (Fig. 2).

Convalescence was uneventful. A moderate hypertension of 110 mm. of mercury diastolic persisted for two weeks and then the pressure returned to normal. A second specimen of urine for pressor amines on the thirteenth post-operative day contained less than 0·1 μg. per ml. (within normal limits).

During the course of a 7-month follow-up the boy has had a normal blood pressure and the changes of malignant hypertensive retinopathy have regressed completely. Growth, which seemed to have been arrested at about the eighth year, has been resumed. He has gained 1 in. in height and 10 lb. in weight.

Discussion

Daeschner, Moyer and Able (1954) have reviewed the clinical features of phaeochromocytoma in children. Although tumours occur at all ages the average age of paediatric cases has been 10 years at the time of diagnosis. Symptoms, however, have usually been present for two years. The hyperten-

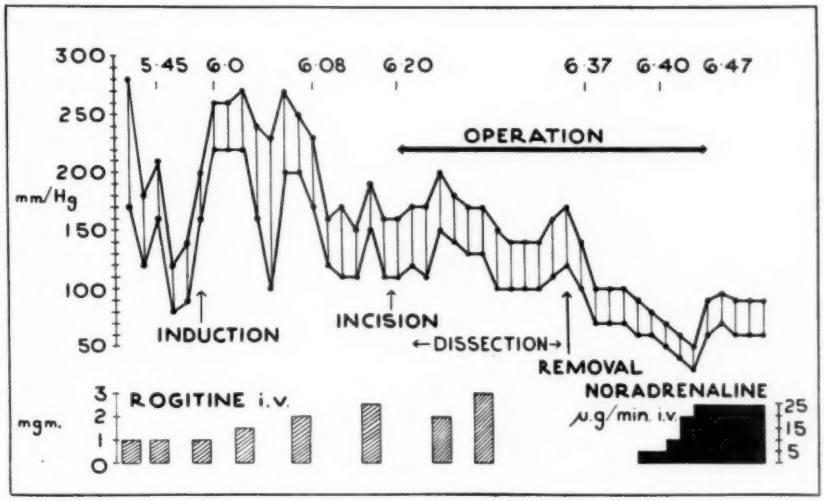

FIG. 2.

sion is usually sustained, malignant retinopathy and sweating are common. Renal function is unimpaired. The hands and feet may resemble acrodynia and it is of interest that recent studies by Farquhar, Crawford and Law (1956) suggest that urinary sympathin secretion may be raised in pink disease. While growth may be retarded by many types of serious illness in childhood this seems to be the first case of phaeochromocytoma in which arrest of growth was such a prominent feature.

Summary

The patient described stopped growing at the age of 8 years and concomitantly developed symptoms suggestive of phaeochromocytoma. When first seen he had malignant hypertension with grade IV hypertensive retinopathy. The diagnosis was confirmed by assay of the urinary excretion of catechol amines which yielded 1 μg./ml. (1,000 μg./24 hr.). A right adrenal tumour was successfully removed and growth appears to have been resumed.

I should like to thank Professor R. E. Tunbridge for permission to publish this case and for his helpful criticism; Mr. D. A. Willoughby for estimation of the catechol amine excretion; Sisters M. Harrison and M. Thwaites for the excellent management of a difficult nursing problem and Miss Campbell for the reproduction of the blood pressure recordings.

References

Daeschner, C. W., Moyer, J. H. and Able, L. W. (1954). *J. Pediat.*, **45**, 141.
Euler, U. S. von (1952). *Scand. J. clin. Lab. Invest.*, **4**, 254.
—— (1954). *Pharmacol. Rev.*, **6**, 15.
Farquhar, J. W., Crawford, T. B. B. and Law, W. (1956). *Brit. med. J.*, **2**, 276.
Helps, E. P. W., Robinson, K. C. and Ross, E. J. (1955). *Lancet*, **2**, 267.
Mégevand, A. and Ferrier, S. (1954). *Ann. paediat.* (Basel), **183**, 337.
Robinson, M. J. and Williams, A. (1956). *Archives of Disease in Childhood*, **31**, 69.
Smid, A. C. and DuShane, J. W. (1955). *Amer. Dis. Child.*, **90**, 81.

OS INTERMETATARSEUM

BY

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From the Royal Portsmouth Hospital

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Variations in the bones of the foot such as accessory bones, fusions and sesamoids occur with some frequency. In the ordinary way the main value in knowledge of these abnormalities lies in differentiation from fractures. Errors arising from the interpretation as fractures of certain radiological appearances, such as the epiphysis at the base of the fifth metatarsal, the os trigonum or an accessory scaphoid, are common examples which can be avoided.

An occasional finding in patients with hallux valgus is the presence of an os intermetatarseum. In the case described below a clinical condition arose in association with this uncommon congenital abnormality and is presented as of special interest.

Case History

A schoolgirl aged 10 was referred for specialist advice with regard to her feet which were somewhat painful on walking and in which there was bilateral hallux valgus deformity with prominence of the medial sides of the heads of the first metatarsals. There was no relevant family history.

On examination she was found to have bilateral hallux valgus with short, abducted first metatarsals not taking their full share in weight bearing. This seemed to be an example of the transverse flat foot of congenital type. However, radiographs showed opacities lying between the first and second metatarsals suggesting the presence of supernumerary metatarsals (Fig. 1). Radiographs of the hands revealed shortening of the middle phalanges of both fifth fingers with varus deformity at the distal inter-phalangeal joints (Fig. 2).

FIG. 1.

FIG. 2.

She was admitted to hospital, the feet explored and the abnormal structures removed. They were elongated processes arising from the medial side of the bases of the second metatarsals and lying on the dorsum of the spaces between the first and second metatarsals. The base, which was bony, was ½ in. in diameter and the structure narrowed towards the distal end which seemed cartilaginous. There was a periosteal covering and opposite

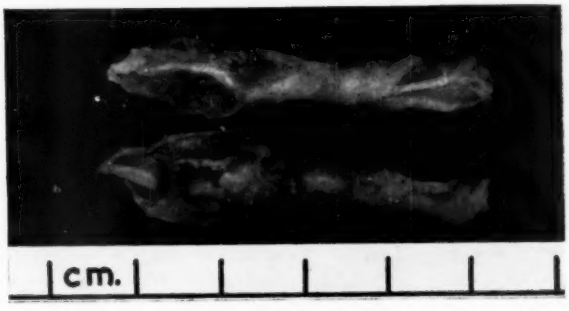

FIG. 3.

FIG. 4.

the necks of the first metatarsals the process ended in a tendinous band which was inserted into the lateral side of the base of the proximal phalanx of the hallux (Fig. 3). Both were removed by dividing the base, which was of bone, and by soft tissue dissection. She was allowed up after two weeks and went home a week later. Six months later there were no complaints with regard to the feet, but the degree of hallux valgus remained unchanged. The radiological appearances are shown in Fig. 4.

Discussion

The intermetatarsal bones removed from this case are among the least common of the accessory bones in the foot. They are situated between the first and second metatarsals, and though sometimes present as a distinct bone are more commonly an elongation from the outer distal end of the first cuneiform or fused with the base of the first or second metatarsals. They are rare and the explanation of their occurrence difficult. The pentadactyl limb is said to be very deeply embedded in the germ plasm of all higher animals and the plan was established when amphibia first emerged long ago. It is, in consequence, somewhat surprising that supernumerary metatarsals occur and that supernumerary digits are relatively common. One explanation of their occurrence is an atavistic return to the many bones found in a fish's fin. Another, possibly more acceptable theory, is that the condition arises by fission of the primary limb buds from which a digit develops.

A CASE OF OSTEOSCLEROSIS WITH HYPERCALCAEMIA AND RENAL FAILURE

BY

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Disorders of calcium metabolism in childhood (except rickets) were regarded as uncommon until the recognition by Lightwood (1952) of the syndrome of 'idiopathic hypercalcaemia of infants with failure to thrive'. Previously there had been occasional reports of children considered to have Albers-Schönberg disease, hypervitaminosis D, primary hyperparathyroidism (Pratt, Geren and Neuhauser, 1947; Philips, 1948) and hyperparathyroidism with renal disease (Andersen and Schlesinger, 1942).

Albers-Schönberg disease is generally regarded as not causing hypercalcaemia, renal damage or ectopic calcification, but these may occur in the other conditions.

Some of the patients described in the literature do not apparently belong to any of these groups. For example, Lightwood (1932) reported a dwarf with mental retardation, osteosclerosis, calcinosis, arterial degeneration and renal damage. Butler (1951) described a similar condition.

Idiopathic hypercalcaemia is regarded by some as occurring in both mild and severe forms, though the latter may be a separate syndrome (Lightwood and Stapleton, 1953). There are patients who show only some of the features of the fully developed severe form and there appears to be a continuous spectrum between the extremes. It is possible that some of the cases described in the older reports were examples of the severe form, and the same is true of this patient.

Case History

L.B.G.H. (No. 11038), a boy, born on September 28, 1952, was admitted on August 6, 1955, aged 2 years 10 months.

The family history was not remarkable; there was one healthy sibling two years older than the patient. His mother had taken the usual supplements during her pregnancy, and delivery was normal at full term.

Except for feeding difficulties and an unusual diet the child developed normally until his final illness. He had bronchitis at the age of 3 months but this soon resolved. He sat up and also cut his first tooth at 7 months and started to walk and talk at 19 months. A photograph of the child at 2 years of age shows a chubby normal infant.

At 2 years 9 months he contracted whooping cough. He lost about 4 kg. in weight during the acute phase, and after the cough subsided his appetite remained very poor and weight loss continued. He complained of itching of the skin, became pale and lethargic, and his parents noticed that he had frequency of micturition. He was constipated.

Six weeks after the onset of the whooping cough a left facial palsy was observed and he was admitted to hospital.

Dietary History. He was breast fed from birth for four weeks, when he was changed to half-cream dried milk because the breast milk failed. At 10 weeks he was changed to full-cream milk.

At 4 months weaning was attempted but he refused all solid foods, and vomited if these were pressed. At 6 months he was persuaded to take a little solid carbohydrate and strained vegetable foods, but at 8 months again refused to take these and continued to exist solely on milk. At 1 year of age he was changed from full-cream dried milk to tuberculin-tested pasteurized cow's milk, and he lived almost exclusively on this for the rest of his life. During the year before admission he had been taking about 3 pints of milk a day. He had been known to take on occasions minute amounts of baked beans, apple, banana, chocolate, toast and butter. He had always refused Ministry of Food orange juice, but had a very occasional teaspoonful of cod liver oil.

On examination, his height was 89 cm. (ideal height for age, 95 cm.), his weight 11·5 kg. (ideal weight for age, 14·6 kg.) and the circumference of the head 50 cm. (normal). He was afebrile. The pulse rate was 110-130/min.

Appearance. His face (Fig. 1) was thin and the forehead was prominent. The muscles were wasted and the skin-fold thickness over the biceps was only 3·0 mm., indicating an almost complete disappearance of subcutaneous fat. The skin was dry and lightly pigmented and showed numerous scratch lesions. There was an obvious weakness of the left side of the face and this

fluctuated considerably from day to day, being sometimes almost absent.

Intelligence. The level of intelligence was good. Formal testing could not be undertaken because of the child's condition, but there was no evidence of mental deficiency; in fact, the general impression was that the child was in advance of his chronological age. He was able to speak quite well, though his voice was husky and he talked little. He knew about 20 letters of the alphabet, and recognized familiar fairy tales.

FIG. 1.—Patient aged 3 years.

Temperament. The boy was difficult to manage, rarely smiled, and cried easily. He was most reluctant to take any food but drank water avidly.

Systematic Examination. The tongue was dry and all the deciduous teeth were present and though worn were not carious.

No abnormality was found in the chest.

The pulse was regular. Blood pressure by auscultation was 190/100 mm. Hg. The heart was enlarged and there was a harsh apical systolic murmur. The peripheral vessels were easily palpable and stony hard to the touch at wrists, elbows, groins and knees.

No abnormality was found in the abdomen.

A left lower motor neurone facial palsy was present. There was a bilateral plastic iritis and the optic fundi showed a hypertensive retinopathy.

Investigations on Admission. A blood count gave: Haemoglobin 6·8 g. %, M.C.H.C. 27·2 %, M.C.V. 78 cubic microns, white cell count 5,500/c.mm. (neutrophils 47%, lymphocytes 50%, eosinophils 3%). Polychromasia was greater than normal and there was some punctate basophilia.

The serum calcium level was 12 mg. % (on two occasions) and serum phosphorus 8·5 mg. %. Blood urea was 133 mg. %. The serum sodium level was 134 mEq./litre, serum potassium 4·3 mEq./litre and serum chloride 92 mEq./litre. The serum bicarbonate level was 15 mEq./litre, serum cholesterol 329 mg. %, serum albumin 4·15 g. %, serum globulin 3·95 g. % and alkaline phosphatase 19 units (King-Armstrong). Electrophoresis showed a small increase in the γ globulin, and a more marked increase in the α_2 and β globulins.

Lumbar puncture and cerebrospinal fluid were normal. The blood Wassermann and Kahn reactions were negative. The urine contained a trace of albumin, a few leucocytes and *E. coli* was recovered on culture. The urinary amino-acid excretion was normal.

Radiographs. The whole skeleton was hypercalcified. The ribs were uniformly opaque whereas the iliac crests showed numerous narrow concentric bands of increased density (Fig. 2). The base of the skull was thickened and there was no remodelling in the femoral shafts. In the metacarpals and phalanges there was a well-marked transverse line of increased density 1-2 mm. wide. Next to it on the epiphyseal side was a similar zone of normal density and then the rest of the bone to the epiphysis was of slightly increased density (Fig. 3).

The position of the dense line was such that it would have been next to the epiphyseal plate at the age of 12 to 18 months. This is the time these epiphyses appear. There were no longitudinal striations in the phalanges.

Calcification of the femoral arteries was visible for the whole length of the thighs and at the knees (Fig. 4).

Epiphyseal development was within normal limits.

Electrocardiograph. This showed sinus rhythm and depression of S.-T. segments in leads V.3 and V.6. Corrected Q-T interval was 0·475 sec. (prolonged). It was considered that these changes could be due to the high serum calcium level.

Progress. A low-calcium diet was started at once, and because of the acidosis oral alkali therapy was given. After three days the serum bicarbonate level was

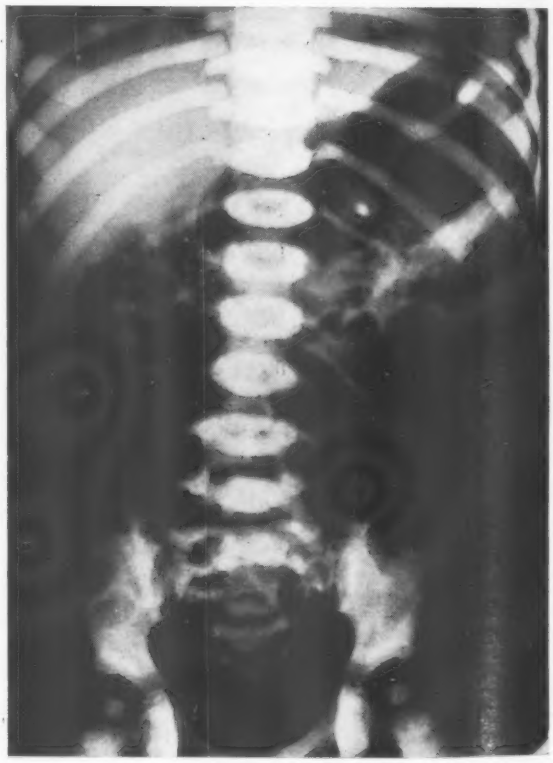

FIG. 2.—Radiograph of the abdomen.

FIG. 3.—Radiograph of the hand.

36 mEq./litre, so the alkali was stopped, but the low-calcium diet was continued for the rest of the patient's life (for intake see Fig. 5).

After one month in hospital the child was a little better. His weight, however, had not risen, but the plastic iritis had improved with local cortisone. It was found that there was rather more pus in the urine, and a course of oxytetracycline was given. The serum calcium had fallen to 11 mg. %, and the blood urea was 180 mg.%. The serum bicarbonate had fallen slowly to 20 mEq./litre.

At the end of the second month there was further improvement, with a gain in weight of 1 kg., though feeding was a perpetual difficulty and three or four hours a day were spent in coaxing scraps of food into the child. Pruritus was troublesome.

The blood pressure was higher, around 240/130, on repeated estimations (by auscultation). The creatinine clearance on two estimations was 2·0 and 2·4 ml./min. Serum calcium was 11 mg. %, the blood urea was 204 mg. %, the serum bicarbonate had fallen to 15 mEq./litre and the serum phosphorus was 8 mg. %. The anaemia was unchanged despite treatment with oral and intramuscular iron.

Balance Studies. The child's condition did not permit continuous urine collection, but several timed samples were obtained and 24-hour excretions calculated from them. The urine calcium estimated in this way varied from 13 to 21 mg./day.

All the stools were analysed over a 10-day period, and it was found that the calcium balance was minus 33 mg. per day.

Cortisone therapy was tried in cautious doses, with a maximum of 15 mg. a day, for three weeks. There was no clinical effect observed but the faecal calcium became even lower during this time, and consequently the cortisone was stopped.

At the end of the third month the child was evidently worse. His weight was falling, and feeding was becoming even more difficult. Serum calcium was 9·8 mg. %, phosphorus 9 mg. %, blood urea 230 mg. %, serum bicarbonate 10 mEq./litre, and serum potassium 3 mEq./litre. Haemoglobin was 3·5 g. %.

Several small blood transfusions were given, and the haemoglobin was raised to 6·0 g. %, with slight improvement in the patient's condition. About this time he developed persistent diarrhoea, for which no infective cause could be found, and various oral electrolyte supplements were needed.

During the fourth month persistent vomiting made it impossible to maintain nutrition and he wasted rapidly. Later, fluid intake was also inadequate, and he became

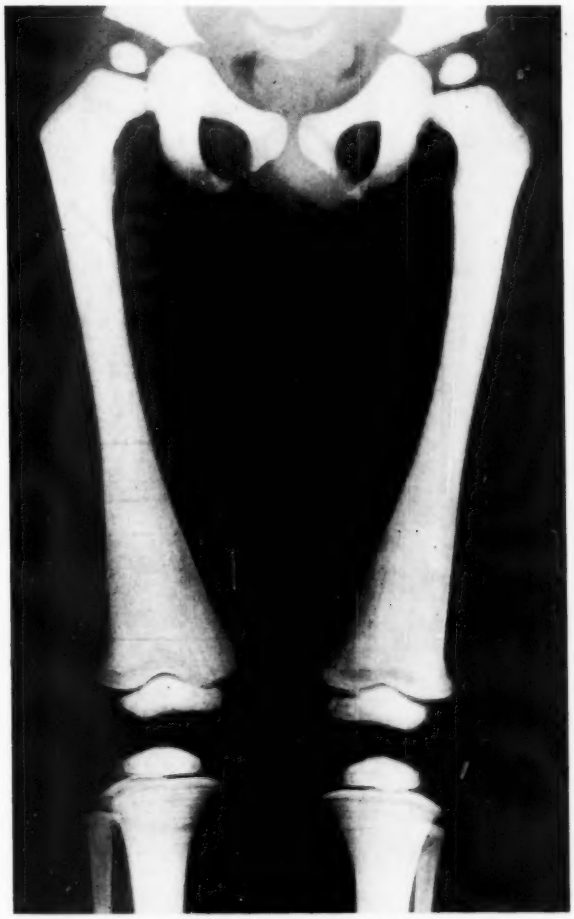

FIG. 4.—Radiograph of the thighs.

dehydrated. Electrolyte solutions were given subcutaneously and intravenously and the dehydration was corrected, but oliguria then developed and the child died a few days later.

Necropsy. Necropsy was performed by Dr. K. Thompson.

Externally the body was that of a slightly oedematous male infant. The right testis was in the inguinal canal, the left in the scrotum.

The heart was enlarged, due to hypertrophy of the left ventricle. There were no valvular defects or septal deficiency. The lungs were oedematous; there was no evidence of purulent infection of bronchi or trachea. The aortic valvular ring was calcified and there was patchy calcification of the wall of the aorta throughout its length, which calcification continued up the carotid arteries and down the iliac arteries into the femoral arteries. No parathyroid bodies were identified.

The liver was enlarged and oedematous, being of a pale buff colour. There was no abnormality in the spleen. Both kidneys were shrunken, the left kidney being less shrunk than the right. The cut surfaces of the kidneys showed blurring of the demarcation line between cortex and medulla, with considerable prominence of the vessels. There was patchy calcification which was both visible to the eye as well as grating to the knife. The renal tissue was oedematous and focally mottled with purple congestion against a grey background, the scarred contracted cortices being irregularly nodular. Both suprarenals showed abundant grey medulla, a clear distinct pigment zone and abundant firm yellow cortex. There was oedema of the stomach and intestines. The stomach contained mucus and streaks of altered blood.

In the head, the brain was oedematous. There was very marked thickening of the base of the skull, particularly of the sella turcica. The tentorium cerebelli contained plaques of calcium forming a rigid sheet in the anterior part.

THE SKELETON. In the ends of the ribs there was no irregularity or excess of the proliferating cartilage. The yellow zone of the provisional zone of calcification was less than 0·5 mm. wide and straight, and no abnormality in the bone structure could be seen. In the lower end of the femur the growth line was irregular, the zone of provisional calcification being wide and irregular and

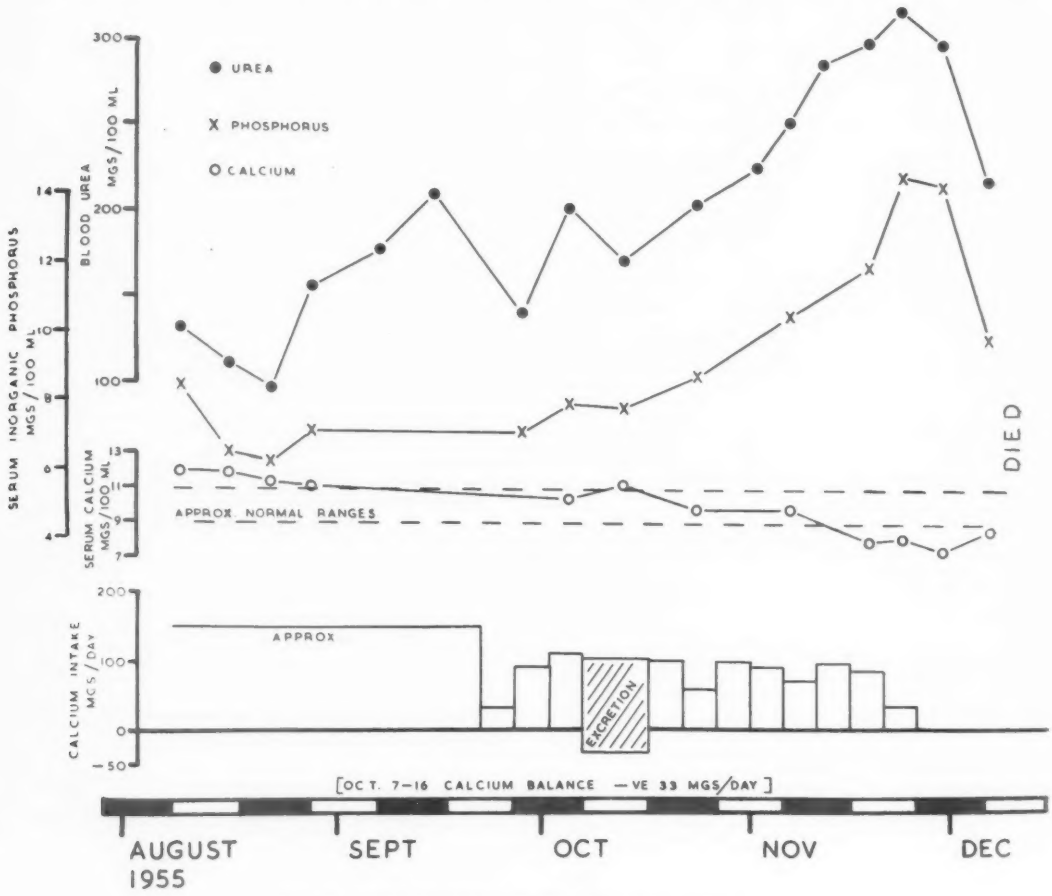

FIG. 5.—Chart of calcium intake and serum analyses.

ther being grey 'epiphyseal' lines showing as ghosts against the purple marrow at the lower end of the shaft. In the iliac crest the bone was in part grey and apparently avascular and in part purple and congested, giving a very mottled appearance to the eye and cutting irregularly to the knife.

Histology. Histological sections were examined by Dr. D. B. Brewer:

KIDNEY. The kidney tissue (Fig. 6) is virtually destroyed. The outer part of the cortex is grossly shrunken. Every glomerulus in this area is completely hyalinized and almost every one is calcified. They are crowded close together. No normal tubules are present. Between the glomeruli are tubules of narrow lumen lined by small cells with dark round nuclei. They resemble closely foetal tubules and in one or two areas are proliferated to form papillary projections into a dilated cyst-like tubular lumen.

There is an irregular zone of cortex which is less affected. There are present here a few normal glomeruli

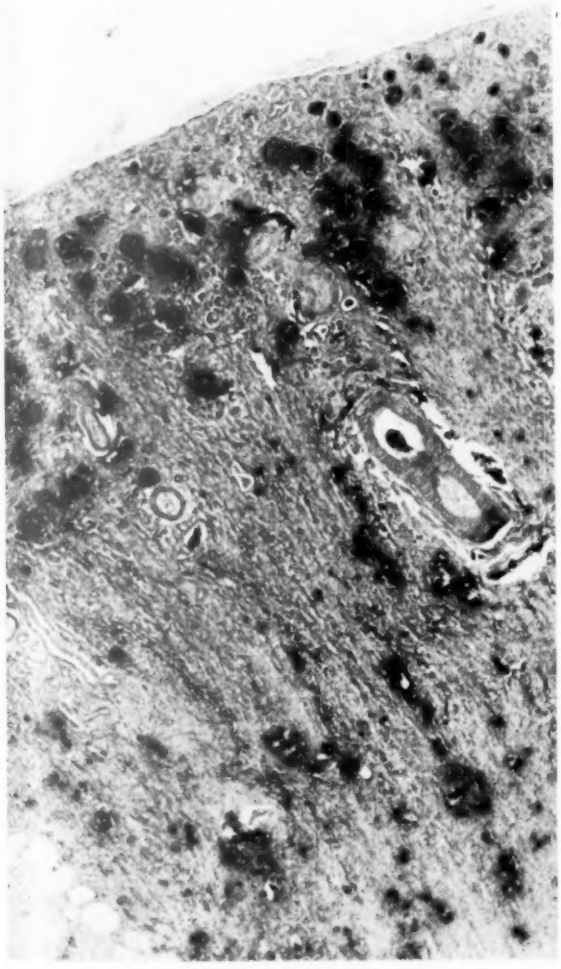

FIG. 6.—Photomicrograph of outer cortical zone of kidney. (×45. H. and E.)

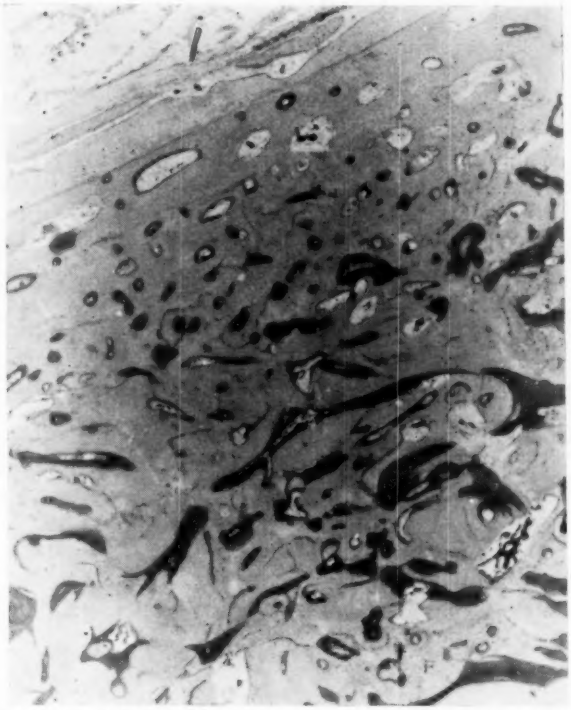

FIG. 7.—Photomicrograph of iliac crest bone. (×23. H. and E.)

but the majority show capsular adhesions with epithelial proliferation about them. Some of these glomeruli are partly hyalinized and one or two show patchy calcification. The tubules in this zone are dilated and lined by atrophic epithelium. In addition to the calcification of glomeruli there are very numerous irregularly distributed areas of interstitial and intratubular calcification particularly numerous in the medulla. Many of the larger arteries also show fine calcification along the elastic lamina. In the arcuate and smaller arteries there is marked intimal thickening by loose cellular tissue that in many cases almost completely obliterates the lumen. The media in these vessels appears normal and there is no intimal thickening in the large branches of the renal artery in the medulla.

MYOCARDIUM. There is moderate diffuse mucoid oedema of the myocardium, and cellular mucoid thickening of the valve cusp. There is also calcification of the valve ring.

FEMORAL ARTERY. Marked crescentic calcification of the media is seen.

SUPRARENAL. The suprarenal is normal, but all the small arteries in the peri-adrenal fat show a slight deposit of calcium on the internal elastic lamina.

LIVER. The sinusoids are only moderately dilated with widespread fatty change.

BONE (RIB AND ILIAC CREST). Both show similar changes though they are more marked in the iliac crest. There is an excessive amount of cancellous bone which, as a result, has become compact bone in the blade of the ilium. The bone is well formed but the lamellar

structure is interrupted throughout by small, irregular, persisting islands of cartilage (Fig. 7).

Discussion

This patient closely resembles the reported cases of the severe form of idiopathic hypercalcaemia except in three particulars, namely, the absence of the characteristic facies and mental retardation (Schlesinger, Butler and Black, 1956) and the late onset of evident ill health.

The severity of the osteosclerosis and ectopic calcification on admission only six weeks after the whooping cough suggests that the pathological processes were far advanced while the child was apparently well. It would appear from the position of the band of increased calcification in the metacarpals and phalanges and the lack of remodelling in most of the femoral shaft that those processes began when the child was about 1 year old.

During the year before admission, his diet had comprised 3 pints of cow's milk a day, which contains:

Protein	56 g.
Fat	63 g.
Calories	1,120
Calcium	2·0 g.
Phosphorus	1·6 g.
Cholesterol	340 mg.
Vitamin D	17 units
Vitamin C	about 15 mg.
Iron	1·3 mg.

The intakes of fat, protein and calories were well enough balanced but the calcium, phosphorus and cholesterol were about twice the amount in the normal diet of a 3-year-old. At the age of 2, the normal retention of calcium is about 90 mg./day, and this falls to 60 mg./day by the age of 3 (Mitchell, Steggerda, Hamilton and Bean, 1945). The vitamin D intake was very low, while the vitamin C intake was probably adequate.

However, on this diet the child appeared to grow well without mental or physical retardation until his final illness.

The serum cholesterol and calcium levels were raised, though not greatly, and both later fell to normal. The other changes in the serum chemistry can be ascribed to the renal failure. The syndrome known as 'renal tubular acidosis' (Lightwood, Payne and Black, 1953) seems an unlikely diagnosis as a very short course of alkali therapy produced a persistent alkalosis. The serum calcium × phosphorus product was 101 on admission and never fell below 73. Presumably it was the high product which caused the excessive deposition of bone salts in ectopic sites, and it seems reasonable to suppose that it was also responsible for the osteosclerosis. The mechanism responsible for the latter must have been more complex as the excess bone appears to be normally calcified osteoid tissue so that the balance of osteoblast-osteoclast activity must have been changed in such a direction as to cause an increase in total bone matrix.

The radiographic changes in the bones resembled those of Albers-Schönberg disease, but the fine longitudinal fissures in the long bones and phalanges (Brailsford, 1953) which occur in that condition were absent. Histological examination of the iliac crest, however, showed persisting islands of cartilage in the excessive cancellous medullary bone such as is seen in the long bones in Albers-Schönberg disease (Warkany, 1954).

Pressure on the facial nerve from expanding bone was presumably the cause of the facial palsy.

The renal lesion was severe and it is not possible from microscopy to form an opinion as to whether chronic pyelonephritis or glomerulo-nephritis might have been present, nor whether the nephrocalcinosis was primary or secondary. The glomeruli of the outer layer of the cortex were nearly all destroyed whereas in the juxtamedullary zone they were less damaged. This differential involvement was noted in a case of severe idiopathic hypercalcaemia described by Lowe, Henderson, Park and McGreal (1954).

The poor response to treatment is not surprising in view of the severe renal damage. A low-calcium diet induced a slight negative calcium balance, which is the usual finding; but small doses of cortisone were accompanied by a fall in faecal calcium (the intake being unchanged), and this is contrary to other reports (Forfar, Balf, Maxwell and Tompsett, 1956).

It is tempting to think that the high calcium and phosphorus product was related to the excessive calcium intake. In the young child, urine calcium tends to be low, and a rise in calcium intake is accompanied by calcium retention (Smith, 1951). It seems reasonable to postulate that calcium retention due to excessive intake might cause an elevation of the serum calcium level of the order which occurred in this case (12 mg. %).

The changes of calcium metabolism in renal failure are usually ascribed to phosphate retention with a secondary fall in serum calcium and consequent failure of calcification of osteoid tissue and secondary hyperparathyroidism. If the serum calcium was kept high as a result of an excessive retention, this sequence might be changed. The high calcium × phosphorus product would allow normal calcification and the high serum calcium prevent secondary hyperparathyroidism.

In adults, renal failure may occasionally be accompanied by osteosclerosis. Crawford, Dent,

Lucas, Martin and Nassim (1954) reported three such cases and commented on the similarity between them and the severe form of idiopathic infantile hypercalcaemia although in those cases the serum calcium was low.

Renal tract infections are common in idiopathic hypercalcaemia, but it is generally thought that primary renal disease is not responsible for the syndrome.

In this patient, however, it seems quite possible that the renal damage was primary and that the subsequent biochemical changes were modified by the high calcium and phosphorus intake, though it is not possible to determine what was the nature of the original renal lesion.

Summary

A patient is described who, after developing normally for nearly three years while living on milk alone, then died of renal failure. There was hypercalcaemia, hypercholesterolaemia, osteosclerosis, gross ectopic calcification, hypertension and severe renal damage. It is suggested that the aetiology in this case might be a primary renal disease with the biochemical changes modified by the diet.

I wish to thank Professor J. R. Squire for helpful advice and permission to publish; Drs. V. M. Crosse and F. L. Ker for permission to publish; and Drs. K. Thompson and D. B. Brewer for the necropsy and histological reports.

References

Andersen, H., and Schlesinger, E. R. (1942). *Amer. J. Dis. Child*, **63**, 102.
Brailsford, J. F. (1953). *The Radiology of Bones and Joints*, 5th ed., p. 613. London.
Butler, N. R. (1951). *Proc. roy. Soc. Med.*, **44**, 296.
Crawford, T., Dent, C. E., Lucas, P., Martin, N. H. and Nassim, J. R. (1954). *Lancet*, **2**, 981.
Forfar, J. O., Balf, C. L., Maxwell, G. M. and Tompsett, S. L. (1956). *Ibid.*, **1**, 981.
Lightwood, R. (1932). *Archives of Disease in Childhood*, **7**, 193.
—— (1952). *Ibid.*, **27**, 302.
—— and Stapleton, T. (1953). *Lancet*, **2**, 255.
——, Payne, W. W. and Black, J. A. (1953). *Pediatrics*, **12**, 628.
Lowe, K. G., Henderson, J. L., Park, W. W. and McGreal, D. A. (1954). *Lancet*, **2**, 101.
Mitchell, H. H., Steggerda, F. R., Hamilton, T. S. and Bean, H. W. (1945). *J. biol. Chem.*, **158**, 625.
Philips, R. N. (1948). *Pediatrics*, **2**, 428.
Pratt, E. L., Geren, B. B. and Neuhauser, E. B. D. (1947). *J. Pediat.*, **30**, 388.
Schlesinger, B. E., Butler, N. R. and Black, J. A. (1956). *Brit. med. J.*, **1**, 127.
Smith, C. A. (1951). *The Physiology of the Newborn Infant*, 2nd Ed., p. 241. Oxford.
Warkany, J. (1954). In Nelson, W. *Textbook of Pediatrics*, 6th ed., p. 1312. Philadelphia.

EFFECTS OF A.C.T.H. ON A CASE OF TUBERCULOUS MENINGITIS

BY

I. M. LECK

From Walsall General Hospital

(RECEIVED FOR PUBLICATION DECEMBER 11, 1956)

Although there are published references to over 200 cases of tuberculous meningitis treated with A.C.T.H., cortisone, or hydrocortisone, very few authors describe the effects of these hormones on patients with over 1% protein in the C.S.F. Kendig, Choy and Johnson (1956) gave cortisone to a child during two periods when her C.S.F. protein was above 5 g. %; the protein content fell below 1 g. within a fortnight each time, and increased again when the first course of cortisone was stopped. Paraf, Paraf and Rapaud (1954) gave A.C.T.H. to patients whose C.S.F. contained up to 3 g. protein/100 ml., but their results, although encouraging, were only reported very briefly.

Case Report

In November, 1952, a girl aged 22 months was admitted to the Manor Hospital, Walsall, with tuberculous meningitis. She was given 45 daily intrathecal injections of streptomycin and a six months' course of P.A.S. and intramuscular streptomycin. She recovered completely, and remained well until nearly 4 years old, when she was admitted to the Walsall General Hospital with a history of fretfulness, headache, vomiting and constipation for a few days. On admission, on December 13, 1954, she was fretful, with slight neck stiffness but no other clinical abnormality. Temperature (normal on admission) was between 99 and 100° F. for most of her first two weeks in hospital. A chest radiograph showed calcification at the right hilum, and a calcified Ghon focus in the left lung which had also been noticed two years before. The C.S.F. contained: white cells, 100/c.mm. (70% lymphocytes), protein, 160 mg./100 ml., glucose, 31 mg./100 ml., chlorides, 740 mg./100 ml. (as Na Cl.), Z.-N. stain, acid-fast bacilli present. Tuberculous meningitis was again diagnosed, and the child was given isoniazid (50 mg. eight-hourly) from December 15, 1954, to July 21, 1955, and intramuscular streptomycin (350 mg. twice a day) from December 15 to June 13. Her clinical condition improved considerably during her first month in hospital, and after two weeks there her temperature became normal apart from rises to 99-99·4° F. once or twice each week.

The C.S.F. was examined weekly. As is shown by the graph, during the first month it became more abnormal; and for three periods between the fifth and fifteenth weeks in hospital it was yellow, with protein about 2 g. %. A course of A.C.T.H. was begun during each of these periods. Within four to 16 days of the start of each course, the C.S.F. protein content fell to 100-300 mg. %, and its fall was especially rapid during the first course (when the initial daily dose of A.C.T.H. was 80 units, not 20 units as in the other two courses). Each time A.C.T.H. was stopped, the C.S.F. protein content increased again within one to six days, although after the third and longest course this increase was relatively small. The protein content increased again when streptomycin

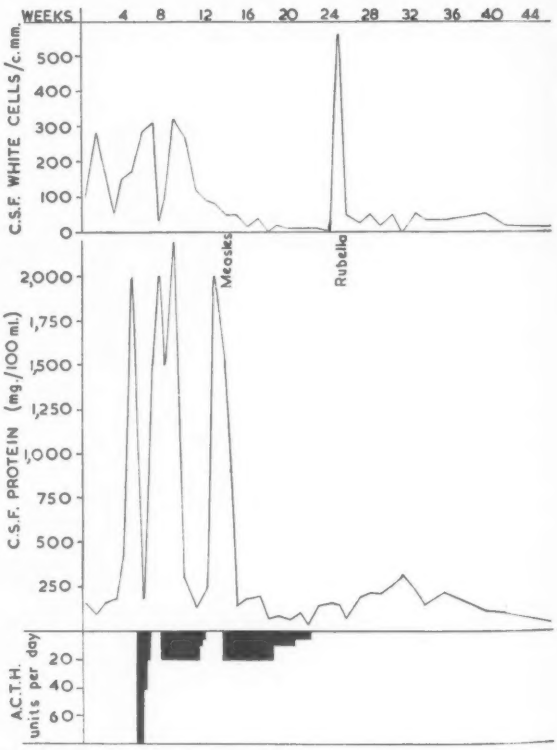

FIG.—C.S.F. Cells and Protein before, during and after treatment with A.C.T.H.

was discontinued, but did not then exceed 320 mg. %, and finally fell spontaneously to normal.

The other contents of the C.S.F. did not fluctuate as widely as the protein. The cells (chiefly lymphocytes) were most numerous (320/c.mm.) during the second great increase of protein, apart from an isolated rise to 560/c.mm. on June 8 (during an attack of rubella). Forty six weeks after admission the C.S.F. was normal, except for 16 lymphocytes/c.mm.

The child's clinical condition bore little relation to these changes in the C.S.F., although during the second great increase of protein her temperature was slightly elevated in the evenings. She had measles after 13 weeks and rubella after 25 weeks in hospital. Otherwise, after the first few weeks she kept very fit. While receiving A.C.T.H. she was euphoric and gained weight rapidly, but her weight fell again after A.C.T.H. was stopped. She was sent for convalescence on July 21 and home on November 24, 1955. When last seen, on May 9, 1956, she seemed quite healthy.

Comment

Three times this child's C.S.F. protein content fell when A.C.T.H. was given and rose when it was stopped. As A.C.T.H. acts on the adrenals, it seems almost certain that these phenomena were due to the anti-inflammatory action of cortisone. This may have reduced the C.S.F. protein content either by relieving intrathecal block or by suppressing the meningeal reaction to tuberculin. The xanthochromia and very high protein content of the C.S.F. could have been due to block, and cortisone may be able to dissolve the tuberculous exudate which causes block (Shane, Clowater and Riley, 1952).

But as the C.S.F. protein content fell so fast when A.C.T.H. was started and rose so fast when it was stopped, and as the child seemed well and C.S.F. was easily obtained on lumbar puncture throughout, there may have been no block. In that case, as it is apparently an intrathecal hypersensitivity reaction to tuberculin that raises the C.S.F. protein content in tuberculous meningitis (Cairns and Smith, 1952), the exceptional rises in this patient's C.S.F. protein content may have been due to exceptional hypersensitivity to tuberculoprotein caused by one attack of tuberculous meningitis following on another. A.C.T.H. may have reduced the C.S.F. protein content by suppressing this hypersensitivity, and the rise in protein each time A.C.T.H. was stopped may have been due to a revival of hypersensitivity. Similarly, Long and Favour (1950) found that in tuberculin-sensitive patients, skin reactivity to tuberculin decreased when A.C.T.H. or cortisone was given, and revived when it was stopped.

If intrathecal block was not present in this case, it was very likely incipient, as a meningeal hypersensitivity reaction intense enough to raise the C.S.F. protein content to 2 g. % would probably soon produce sufficient exudate to cause block. To avoid this, all patients whose protein content is so high should perhaps be given A.C.T.H. (or cortisone), in the hope that it will disperse any exudate and/or suppress the intrathecal tuberculin reaction by which such exudate may be produced. As this patient's C.S.F. protein content rose rapidly when the first and second courses of A.C.T.H. were stopped, it seems that this may need to be given for two or more months if it is to have a lasting effect.

I am grateful to Dr. J. M. Garvie for permission to report this case and for his very helpful advice.

References

Cairns, H. and Smith, H. V. (1952). In *Modern Practice in Tuberculosis*, 1st ed., vol. 2, p. 364. Ed. Sellors, T. H., and Livingstone, J. L. London.

Kendig, E. L., Jr., Choy, S. H. and Johnson, W. H. (1956). *Amer. Rev. Tuberc.*, 73, 99.

Long, J. B. and Favour, C. B. (1950). *Bull. Johns Hopk. Hosp.*, 87, 186.

Paraf, J., Paraf, M. and Rapaud, G. (1954). *Bull. Soc. méd. Hôp. Paris*, 70, 1165.

Shane, S. J., Clowater, R. A. and Riley, C. (1952). *Canad. med. Ass. J.*, 67, 13.

TRANSIENT RASH AND HAEMATURIA AFTER EXERCISE AND EMOTION

BY

R. S. ILLINGWORTH and K. S. HOLT

From the Children's Hospital, Sheffield

(RECEIVED FOR PUBLICATION FEBRUARY 12, 1957)

Now and again one is faced with the problem of a case of haematuria whose cause thorough investigation fails to determine. Many such cases are termed 'essential haematuria', and almost every volume of the *Quarterly Cumulative Index Medicus* gives one or more references to papers about this mysterious condition.

Below is an account of a child who had frequent attacks of haematuria immediately following a rash which was largely erythematous and partly urticarial, and which initially was regarded as an example of allergic haematuria.

Case Report

The patient, a girl aged 5½ years, was brought to the Children's Hospital, Sheffield, on account of seven attacks of haematuria in the previous four months. In all the attacks blood had been passed in single specimens only. There had been no history suggestive of nephritis, no puffiness of the eyes and no other symptoms except dysuria in some of the attacks of haematuria. She was otherwise well and full of energy.

On examination the girl was well and afebrile. She weighed 42 lb. The blood pressure was normal (110/70 mm. Hg). There were no abnormal physical signs. The erythrocyte sedimentation rate was 13 mm. in one hour. The blood urea was 25 mg. %. There was a trace of albumin in the urine (25 mg. %), but the centrifuged deposit was normal. Nephritis was thought to be unlikely, and she was admitted for imvestigation.

Her previous and family history were irrelevant. She had been a premature baby, weighing 4 lb. 8 oz. Her development had been normal, and her intelligence was average. She had five siblings, and neither they nor her parents had suffered from any known allergic conditions.

On further questioning after admission the child stated that for half an hour before the first attack of haematuria she had had a measles-like rash, and that a rash had appeared before each of the six other attacks. There had also sometimes been a rash without subsequent haematuria, but never haematuria without a preceding rash. The mother added that her tongue was notably red in attacks. She always knew when haematuria was going to occur, because of the prodromal rash.

The history was suggestive of allergic haematuria, and a confident diagnosis of this condition was made after we had observed the rash.

We saw a rash (Fig. 1) on 22 occasions in her 13 weeks in hospital: on 11 of these occasions she developed naked-eye haematuria within half an hour of the appearance of the rash. The more extensive the rash, the greater was the frequency with which haematuria followed it. On two occasions she had haematuria without a preceding rash, though it is likely that a rash had occurred without being noticed. On each occasion the rash was a diffuse patchy erythema, with occasional wheals, which covered the trunk and face, and to a lesser extent the limbs. We could find no haemorrhagic element in the

FIG. 1.—Rash immediately preceding haematuria.

rash, even on examination with a hand lens, nor was there bleeding elsewhere, such as epistaxis or melaena.

During the attacks the blood count, including the eosinophil and platelet count, the bleeding and coagulation time and the capillary fragility tests were normal. There was no elevation of temperature in the attacks. When the haematuria occurred, there was only a small amount of albumin and there were no granular or cellular casts in the centrifuged deposit.

We were impressed by the short duration of the rash. For instance, at 9 a.m. one day the skin was clear; at 10 a.m. she developed a rash, and the tongue and palate were red, with prominent papillae: the rash lasted 30 minutes. At 10.45 a.m. there was macroscopic haematuria. At 11.15 a.m. the urine, including the centrifuged deposit, was normal.

Investigations on Admission. A throat swab grew β haemolytic streptococci, group A.

The A.S.O. titre was 100. Tests for C-reactive protein were negative, and mucoprotein was 1·9 mg./100 ml.

A Mantoux test (1 in 1,000 O.T.) was negative. Radiographs of the chest and abdomen were normal.

A blood count gave: 14·5 g. %; R.B.C.s 4,100,000 per c.mm.; W.B.C.s 8,000 per c.mm. (polymorphs 58%, eosinophils 2%, basophils 1%, lymphocytes 30%, monocytes 9%); platelets 360,000 per c.mm.; bleeding time 2½ minutes; coagulation time 3 minutes; blood urea 35 mg. %; the E.S.R. 9 mm. in one hour. The Wassermann and Kahn reactions were negative. Isoagglutinins and cold agglutinins were absent.

Serum proteins totalled 6·5 g. % (albumin 3·8 g. % and globulin 2·7 g. %). Electrophoresis showed some increase in α_2 and β globulin, but no cryoglobulin.

Skin tests for common allergens were negative.

Spectroscopic examinations of urine in attacks showed no haemoglobinuria.

Shortly after her admission we took her to the theatre for cystoscopy immediately after she had passed a grossly bloodstained specimen of urine, only to find that the urine had returned to normal. As mentioned below, this rapid clearing of the haematuria may have been due to premedication with atropine. Further cystoscopy was not thought to be justified and for the same reason sigmoidoscopy and proctoscopy were not carried out.

We began a series of elimination diets, but made no progress in elucidating the cause, for attacks continued to occur irrespective of the diet which she was having.

It was then realized that there was an emotional factor in the attacks, for on at least three occasions the rash developed immediately after a venipuncture, and on three or more occasions during the professorial ward round. Her mother then said that over-excitement was a factor in the production of the rash, for she had noticed that it had preceded at least three of the attacks.

After three months' observation and study, we felt that we were making no progress in the elucidation of the problem, and once more discussed the matter with her mother who then remarked that she was sure that she knew why the girl had haematuria: it was caused, she said, either by over-excitement or over-exertion. We then tried the effect of exertion and promptly precipitated an attack. This was repeatedly confirmed, and at a clinical meeting of the Sheffield Regional Paediatric Society we showed the girl without a rash and with normal urine, and then caused two medical students to exercise her in the adjacent park. She returned 20 minutes later with a profuse erythematous rash and gross macroscopic haematuria.

Discussion

At first it seemed likely that this child was suffering from allergic haematuria. Haematuria has been known to follow injections of T.A.B. (Coca, 1930), tetanus antitoxin (Rhodes, 1937), dust extract (Adelsberger, 1931), insulin (Henderson, 1927), the ingestion of codfish (Miller and Uhle, 1939), milk (Kittredge and Johnson, 1949), goat milk (Blaustein, 1926), potassium iodide (Withers, 1956) and the inhalation of allergens (Thomas and Wicksten, 1944). The subject is reviewed by Urbach and Gottlieb (1946). Subsequently we discarded the diagnosis of allergic haematuria.

It was realized that the rash was probably identical with urticaria of nervous origin described by Grant, Pearson and Comeau (1936). Our patient's rash was similar to that described by these authors in its distribution, appearance, precipitation by exercise and emotion, and its transience. Warmth also precipitated the rash but it was a less powerful stimulant than either exercise or emotion. The rapid disappearance of the rash and haematuria just before cystoscopy may have been due to premedication with atropine (gr. 1/100, 0·65 mg.). We tried the effect of giving atropine (gr. 1/150) just before exercise, and the resulting rash was not followed by haematuria. Atropine did not abolish the attack as in the case reported by Grant *et al.* (1936) but modified the attack as in the case reported by Herxheimer (1956). We applied a 10% aqueous solution of atropine sulphate to the skin, and found that it abolished the rash in that area just as it did in the case reported by Herxheimer (1956).

It appears, therefore, that the rash observed in our patient is almost certainly identical with urticaria of nervous origin. The association of haematuria with this condition is not mentioned by Herxheimer (1956) or Morgan (1953), nor could we find any paper referring to it in a search through the *Quarterly Cumulative Index Medicus*. One of the original writers to describe urticaria of nervous origin is unaware of any connexion between this condition and haematuria (Grant, 1956). Transient haematuria can occur apparently after exercise. Boone, Haltiwanger and Chambers (1955) described football haematuria. Six out of 37 football players showed gross but transient haematuria after a strenuous

game. No mention is made, however, whether any of these players had a rash.

Summary

We have described a 5-year-old child who had repeated attacks of a rash followed frequently by haematuria. These attacks immediately followed emotion or exercise.

References

Adelsberger, L. (1931). *Dtsch. med. Wschr.*, **57**, 585.
Blaustein, N. (1926). *J. Urol.* (*Baltimore*), **16**, 379.
Boone, A. W., Haltiwanger, E. and Chambers, R. L. (1955). *J. Amer. med. Ass.*, **158**, 1516.
Coca, A. F. (1930). *Bull. N.Y. Acad. Med.*, **6**, 593.
Grant, R. T. (1956). Personal Communication.
——, Pearson, R. S. B. and Comeau, W. J. (1936). *Clin. Sci.*, 2, 253.
Henderson, J. (1927). *Brit. med. J.*, **1**, 231.
Herxheimer, A. (1956). *Clin. Sci.*, **15**, 195.
Kittredge, W. E. and Johnson, C. (1949). *New Orleans med. Surg. J.*, **101**, 419.
Miller, M. W. and Uhle, C. A. W. (1939). *Int. Clin.* n.s. 2, 3, 183.
Morgan, J. K. (1953). *J. invest. Dermat.*, **21**, 173.
Rhodes, J. (1937). *J. Urol.* (*Baltimore*), **38**, 410.
Thomas, J. W. and Wicksten, V. P. (1944). *Ann. Allergy*, 2, 196.
Urbach, E. and Gottlieb, P. M. (1946). *Allergy*, 2nd ed. New York.
Withers, O. R. (1956). In *Current Therapy*, 1956, ed. by Conn H. F. Philadelphia.

BOOK REVIEWS

Handbook of Pediatric Medical Emergencies, 2nd ed. By ADOLPH G. DESANCTIS, with the collaboration of CHARLES VARGA and ten contributors. (Pp. 398; 73 figures. 46s.) London: Henry Kimpton. 1956.

Emergencies in children tend to be emergencies indeed, and with the increase of effective drugs, and of exact methods both of diagnosis and of controlling treatment, the need for a practical book on paediatric emergencies has increased. This book provides for that need admirably. It goes a little beyond the requirements of the emergency, but does not set out to be a complete textbook of paediatrics. It does, however, cover the whole field, from the point of view of the house physician, registrar, or general practitioner, rather than from that of the visiting paediatrician or surgeon.

The sections on water, electrolytes, diarrhoea and vomiting, etc., on which so much advance has been made, are most useful. In all sections there is a proper stressing of those clinical findings on which emergency diagnosis must be based, as opposed to the stress on laboratory investigations so often found in American textbooks. The details of dosage are full and simple.

Perhaps the best feature of the book is the section on paediatric procedure (vein puncture, paracentesis, oxygen therapy, marrow puncture, etc.), which is profusely illustrated and so made instantly and completely comprehensible. Being printed on highly-glazed paper, the book is heavy, and unless it is kept on the spot where emergencies are seen it is likely not to be there when wanted. But it could lie on the back seat of a car without inconvenience.

The sections on the treatment of poisoning is a little old-fashioned. Treatment by antidotes, although logically excellent, is in practice disappointing. Better results are given by the more general treatment started in this country by Dr. Marriott at the Middlesex, concentrating on the treatment of the very few processes by which poisoned patients die, and keeping them alive until they get the better of the poison. There is, however, an excellent appendix on the chemical nature of poisonous substances met with in the home and garden. It is always valuable to know with what one is dealing.

The emergencies dealt with are, for the most part, common to all countries and to all people, without any special American aspect. Such things as snake-bites are not so common in this country, and although details of treatment are superfluous it is perhaps comforting to appreciate that one is not likely to be bitten from behind by a black widow spider in the closet in this country.

Altogether this book deals thoroughly with a subject on which a book is welcome.

Paediatric X-ray Diagnosis, 3rd ed. By JOHN CAFFEY. (Pp. xxiv.+1059; 1,267 figures. 210s.; $28.00). Chicago: The Year Book Publishers; distributed in the U.K. by Interscience Publishers. 1956.

Dr. John Caffey's book has been the standard work of reference for all those interested in children's radiographs since its first appearance in 1945. The many excellent qualities of the book must largely explain the fact that it still has no real rival in the English language despite the great extensions of scope and knowledge of paediatric radiology there have been in the past decade.

The present edition is a worthwhile advance on its predecessor. A variety of new subjects has been included and many sections in the last edition have been enlarged. The text has been expanded by nearly 200 pages. It is easy to read and understand. The illustrations have been increased in number by 228. They are again of the highest quality. The book is heavy (6 lb. 8½ oz.) and the binding does not seem to be quite strong enough for such a load, particularly when the high cost is borne in mind.

Dr. Caffey is at his best when dealing with bone and the various sections devoted to normal or abnormal bone make up almost exactly half the book. The odd radiological appearances produced by normal anatomical variations and the importance of not confusing these with pathological changes are, once again, rightly stressed. It is to the sections on bone and its diseases that the experienced paediatric radiologist will still find he likes to refer. He will find less of practical value in the other sections though these are full of information for the student and the relatively inexperienced.

The comparative weakness of such sections as that on heart disease is due partly to the omission of the details of the special techniques on which paediatric radiology now depends so much. Dr. Caffey regards most of the techniques as beyond the scope of the book. This may be so, but the omission of practical details of how such techniques are performed and of how their results are interpreted together with a lack of detailed consideration of differential diagnosis leaves little of value to anyone with the responsibility of making a precise diagnosis in a difficult case.

It seems a pity that on one of the few occasions when there is a description of the technique of an investigation —encephalography—few of the practical details which make all the difference between success and failure are mentioned, and, in any event, the method described is completely out of date and would be best avoided by anyone undertaking this examination.

The few paragraphs on partial thoracic stomach are of

interest in showing some reconciliation of American and British views on this important subject but there is still a long way to go. Dr. Caffey regards chalasia as the principal cause of haematemesis in infants, whereas workers in this country doubt the existence of chalasia as an entity, but believe that children in whom this diagnosis is made have, in reality, a hiatus hernia.

Hirschsprung's disease is a term not used in the book, but the section on aganglionic megacolon is an adequate summary of present knowledge of this disease with one important exception. There is no mention of the necessity, if diagnosis is to be reliable, for carrying out the barium enema examination at a time when the child has not been having bowel wash-outs. Moreover, if this simple precaution is observed, a correct diagnosis of Hirschsprung's disease can nearly always be made with confidence in the first few days or weeks of life, although Dr. Caffey seems to think it is not possible to make the diagnosis radiologically during the neonatal period.

Criticisms can always be made of any medical textbook, particularly those of omission. Dr. Caffey's book contains a wealth of information clearly and pleasingly put forward. It must be one of the best standard works on any medical subject. It is most strongly recommended and should be available to all paediatricians and all radiologists.

Essentials of Paediatrics for Nurses. By I. KESSEL. (Pp. 204+Index; illustrated. 21s.) Edinburgh and London: E. & S. Livingstone. 1957.

This book is produced on good paper, has many very excellent illustrations, is well bound and has the additional advantage of an attractive paper cover. The information it contains is never inaccurate but is at times vague and at others outside the scope and understanding of the generality of nurses; scientific terms are often inadequately defined, and the general description of many conditions bewildering. The illustrations, though well done, are for the most part chosen for rarity rather than teaching value. For instance, of the nine illustrations in the chapter on 'Disorders of the Alimentary Tract' one relates to a swallowed coin, two to oesophageal atresia, three to hiatus hernia and three to trichobezoar. It is doubtful whether nurses in training will find in this book adequate answers to their numerous questions on the medical aspects of their work.

A Textbook on the Nursing and Diseases of Sick Children for Nurses, 6th ed. By various authors. Edited by ALAN MONCRIEFF and A. P. NORMAN. (Pp. xvi+777; 146 figures. 50s.) London: H. K. Lewis. 1957.

The current controversy as to whether nurses should be taught more or less medicine has not yet been settled, but the nursing of children is so important that it would be contrary to the interests of the patients to neglect the fundamentals necessary to understand why the child is ill. These fundamentals are concisely and lucidly explained in this book, which has reached its 6th edition.

As before, it is the work of a team of contributors from The Hospital for Sick Children, Great Ormond Street, and represents the practice of that hospital.

The first third of the text describes nursing and general considerations: it includes chapters on the normal child, preventive medicine and care of the ill child at home. The rest of the book considers feeding and the diseases both medical and surgical affecting children.

The descriptions are clearly set out and although rare conditions are mentioned briefly, the emphasis is on the maladies most commonly encountered.

The illustrations are well chosen, and the whole volume has been extensively revised, while new chapters have been added, bringing it up to date.

It maintains the high standard of previous editions, and can be recommended as the best text of its kind in this country.

Advances in Pediatrics, Vol. IX. Edited by S. Z. LEVINE. (Pp. 336. 68s.) London: Interscience Publishers; Chicago: Year Book Publishers. 1957.

This latest volume of *Advances in Pediatrics* contains the usual seven authoritative monographs written by people who have distinguished themselves in the field of which they write. The subjects are post-maturity by Stewart Clifford, the gamma globulins by Janeway and Gitlin, thyroid disorders by Reilly, familial dysautonomia by Conrad Riley, the use of fluoride compounds in the prevention of dental caries by Edward R. Schlesinger and David B. Ast, coagulation disorders in infancy and childhood by Schulman and Carl Smith—all these from the United States—and coeliac disease by the Dutch workers Weijers, Van De Kamer and Dicke. It will be seen at a glance that there is something here for every sort of paediatrician, indeed it might be said that everything in the volume is for every sort of paediatrician. The bones of their subjects are laid bare by the writers in a masterly fashion and with deceptive simplicity, so that those reading the book will have no excuse for not being thoroughly on top of at least seven paediatric subjects.

It would be difficult, and indeed invidious, to single out any one of these articles for especial comment; there is something for the clinician, the neurologist, the nutritionist, the biochemist, the endocrinologist, the haematologist and those interested in preventive dentistry and perinatal morbidity. What more could be gathered together in one so small volume?

Pre- and Postoperative Care in the Pediatric Surgical Patient. By WILLIAM B. KIESEWETTER. (Pp. 347; 49 figures. 52s., $7.00.) Chicago: Year Book Publishers; distributed in the U.K. by Interscience Publishers. 1956.

This small book has been written by 16 contributors from the Children's Hospital of Pittsburgh and has been 'written with the occasional paediatric surgeon in mind'. The outline form adopted for ease of reference gives little pleasure to the reader. Ease of reference is not obtained by the inclusion of funnel chest, thyroglossal cysts and lateral cervical cysts and fistulae in the chapters headed 'abdominal'. It is surprising to find no reference to intestinal obstruction in the index and the occasional paediatric surgeon is expected to know the exact cause

of the obstruction in order to learn the pre-operative care. Again, the adoption of alphabetical arrangement of subjects in the thoracic chapter means jumping from one system to another. It would have been better if the lesions had been grouped under headings such as the diaphragm, trachea and lungs, heart and great vessels and oesophagus.

Apart from criticisms of arrangement the book has some value for surgeons who are faced only occasionally with the surgical treatment of the infant and child, while it will also be useful to house surgeons as a manual of pre- and post-operative treatment.

Pathologie und Klinik der Cytomegalie. By GERHARD SEIFERT and JOHANNES OEHME. (Pp. viii+120; 47 figures. DM 19.60.) Leipzig: Georg Thieme. 1957.

Cytomegalic inclusion disease was discovered in 1881 by Ribbert, and although Farber and Wollbach stressed the frequency of symptomless cytomegalic inclusions in duct-cells of salivary glands and their similarity to those found in a disease of rodents it is only in recent years that a more general interest in this disorder has been shown. The reasons are to be found in several reports on the generalized form of the disease, the possibility of confusion with haemolytic disease of the newborn and in the remarkable syntropy with other diseases, such as pneumocystis-pneumonia. The present monograph is the result of several years' collaboration of a pathologist and a paediatrician. It is based on a detailed study of 83 personal cases and a review of 173 described in the literature, in addition to 20 observed in adults. Morphology, histochemistry and localization in individual organs are well described. The description of neonatal inclusion hepatitis deserves special mention. In the following chapters the clinical symptomatology and differential diagnosis are discussed. Here the description of a collector for the parotid secretion should prove useful. The differential diagnosis from haemolytic disease of the newborn, toxoplasmosis, listeriosis and syphilis is given in the form of a table. The confusing nomenclature of encephalitis in cytomegalic inclusion disease on one hand and inclusion encephalitis on the other is rightly stressed. The isolation of the virus by Smith and by Weller and its propagation in human fibroblast cultures are recorded and the curious fact mentioned that in these cultures only intranuclear and no cytoplasmic inclusions were seen. The paper, print and illustrations of the book are faultless.

Pica. By MARCIA COOPER. (Pp. viii+114. 27s. 6d.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

Paediatricians see occasional children with the strange habit of eating dirt but the author of this monograph reports that over one-fifth of pre-school children attending a welfare centre associated with the Johns Hopkins Hospital are thus afflicted. She finds it associated with 'hyponutrition' and of course it carries a high risk of lead poisoning. Her studies roam back into history and widely into veterinary matters, anthropology and soil chemistry. The book will tell the reader everything he is ever likely to want to know about pica except what to do about it, and the word 'treatment' does not appear in the index. The price is high, and a slightly pretentious list of publication details includes the fact that the type page is '23 × 37 picas'.

Soranus' Gynecology. Translated by OWSEI TEMKIN. With the assistance of Nicholson J. Eastman, Ludwig Edelstein and Alan F. Guttmacher. (Pp. xlix+258. 40s.) Johns Hopkins Press (London: Cumberlege). 1956.

The spate of publications on matters of medical historical interest seems to indicate that the more rapidly we go forward in the conquest of disease, the more willing we are to look back upon the foundations of modern medical knowledge and practice.

This is the first complete English translation of " Soranus' Gynecology". It has been based on Ilberg's Greek text by a group of Americans led by Drs. Temkin, Eastman, Edelstein and Guttmacher and was started in the 1930s but, because of the second world war, it has only recently been completed.

Soranus practised medicine in Rome in the early second century A.D. He wrote nearly 20 works on a wide range of subjects of which his *Gynecology* is by far the most important. It is divided into four books which deal with normal and abnormal gynaecology and midwifery, but Book II contains 46 pages concerned solely with the care of the newborn and is, therefore, the most interesting section for paediatricians. Indeed, it set the standard for all writings on mothercraft for the next 1,500 years and some of the ideas set down by him survive to this day, whereas others, such as the salting of the newborn and the technique of swaddling, have mainly been discarded. Some, having been eclipsed, are now in vogue again for Soranus recommended that in most cases the newborn should be allowed to rest and 'abstain from all food up to as long as two days . . . unless the appetite indicate an earlier time'. Perhaps the famous nail test for assessing the quality of breast milk, which was copied from book to book until the end of the eighteenth century, will become popular again now that science has defined the wide range of composition of milk from different mothers.

The modern reader will find much of interest throughout the whole book. The lucidity and the easy flow of the text are a tribute to the translators, and the abundant common sense repeatedly expressed throughout the work is clear support for Soranus' reputation as the most learned medical writer of antiquity.

Mental Health and Education in Hong Kong. By K. E. PRIESTLEY and BERYL R. WRIGHT. (Pp. 97. 7s. 6d.) Hong Kong University Press (London: Cumberlege). 1956.

These six lectures, followed by a report of the subsequent group discussions, were given by the Professor of Education and the Lecturer in Educational Psychology in

the University of Hong Kong; they describe the way the problem of mental health, with particular reference to child guidance and the establishment of a clinic, is being tackled in circumstances other than our own. In an informative and interesting manner it describes these circumstances, and helps to remind us how relative our concepts are, particularly those concerning normality.

The wide range of individual differences existing within the range of normality is well emphasized by Miss Wright; however, she might also have included the important point that research has shown us that many of the so-called abnormalities of children are only apparent and pass with increasing age. Her assertion that maternal deprivation necessarily results in permanent personality damage is not valid, and there is now further evidence showing that the dangers have been overstated in the past.

Professor Priestley rightly stresses the scientific approach to mental health and the need for research, though this is not compatible with Miss Wright's subjective observations, for they require much more rigorous verification than the comments of parents and teachers which she suggests; scientific psychology aims at description and explanation, common-sense psychology seeks to understand. That the 'West may have a great deal to learn from the East' is certainly true.

Changes in Body Water Compartments During Growth. By BENT FRIIS-HANSEN. (Pp. 68; 12 figures, 21 tables. Dan. Cr. 25.00.) Copenhagen: Ejnar Munksgaard. 1956.

This is a monograph of some 67 pages in which the author reports a study of the total body water and the extracellular body water, intracellular water being calculated by difference. He has used, as material, 93 subjects varying in age from birth to 16 years.

In the first chapter, after a short but interesting historical note, he discusses the methods for both estimations and comes to the conclusion that the answer varies according to the method used. He has used therefore a method to suit his own convenience. For total body water he has used the uncorrected volume of dilution of heavy water and for the extracellular water, he has used the thiosulphate volume of dilution. His normals have been obtained from various hospitals in Boston and the Rigshospital in Copenhagen.

A fair proportion of the work is devoted to a statistical study of these results in an endeavour to discover what constants, if any, would enable one to determine the size of the water compartments from either age, weight, height or a combination of these. There does not appear, however, to be a formula which is valid. It was found that the total body water expressed as a percentage of the body weight decreases with each age group from 77·6 at birth to 58·4 in adolescence. It is therefore possible to get an approximate value of the total body water using the age and weight. The extracellular water decreases in the same manner with age, and again the percentage of the body weight, varied according to age, gives one the most accurate measurement. On the other hand, the intracellular water remains relatively constant, increasing slightly if anything during the first years of life when expressed as a percentage of the total body weight.

In the last chapter there is some discussion of the meaning of these results. The main conclusion is that in all mammals there is a progressive 'drying out' as they develop from the foetal to the adult stage.

This book contains a considerable amount of work, much of which has been published in separate papers and to anyone requiring standards for body fluids it will prove of great value. There are one or two unfortunate errors in the tables and a certain number of misprints in the text.

All Our Children. A Book for Parents. By SIMON YUDKIN. (Pp. x+201. 12s. 6d.) London: Max Reinhardt. 1956.

Although this book is written specially for parents, it will be of great interest to teachers, family doctors, paediatricians, and in fact to anyone who is closely associated with the developing child.

The great decrease in prolonged illness in early life has made the paediatrician increasingly aware of the many problems associated with the emotional development of the child. These problems have themselves increased in complexity because of the profound and rapid social changes in the last few years, and the general background of unrest and insecurity in the world.

Much valuable help will be obtained from this book in dealing with these problems of childhood and adolescence perhaps leading to the prevention of more serious disorders which can only be dealt with by a trained psychologist.

Dr. Yudkin stresses the great individual variations that occur in the intellectual and emotional growth of children who so often fail to conform to the rigid standards expected of them by educationalists, or to fit into the plan of their lives laid down for them in advance by their fond parents. Mistakes by parents are inevitable, but Dr. Yudkin points out that the lasting effect of single mistakes has received undue emphasis, too much attention often being paid to the science of 'diaperology'.

This very readable and well-produced book should be studied by everyone interested in the development of children. There can scarcely be a subject of greater importance.

Ninth International Congress of Paediatrics

The ninth International Congress of Paediatrics will be held in Montreal, Canada, from July 19 to July 25, 1959, under the chairmanship of Dr. Alan Ross, Professor of Pediatrics, the Montreal Children's Hospital, Montreal 25, Canada.

ON GROWTH AND DEVELOPMENT*

PART I. ANATOMICAL CONSIDERATIONS

BY

RUSTIN McINTOSH

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The invitation to give the Sir Leonard Parsons lectures carries high honour. For me the invitation has a particular appeal, the honour a special worth, because I had the privilege of knowing Dr. Parsons for some 20 years. Our first encounter was in Sweden in 1930 when we happened to be making our way toward the International Paediatric Congress by the leisurely means of the Gothenburg-Stockholm canal ship. Professor Smellie remembers it well, too, for he accompanied Dr. Parsons and, like most of the passengers on board, was exploring those unfamiliar Scandinavian waterways for the first time. In that heterogeneous assembly of tourists, professional people, and business men who comprised the passenger list, the customary inclination of the individual traveller to keep to himself, to play his hand cautiously while fixing an appreciative eye on the scenery and awaiting the turn of events, was on its way to establishing standard procedure. Indeed, one might at first have inferred that the only plausible bonds among the various groups were membership in the human race and a common admiration for the beautiful countryside bordering the Gotha Canal—scarcely enough, indeed, to provide footbridges of friendliness across the chasms of reserve which separated one from another. Not so, however, for the Englishman of alert and energetic air, remarkably youthful for one whose hair was snow-white, about whom a cluster of friends seemed to be constantly growing and who had the knack of expressing, or transmitting somehow without verbal expression, a sincere interest in the aims and concerns of even the newest acquaintance. We met by the process of mutual self-introduction, still much less of a shock for an American, I suppose, than for a Briton in spite of the changes in social custom that have taken place over the past generation. In my luggage I had with me a letter of introduction written on my behalf by my former chief, Dr. E. A. Park, which I had counted on presenting in due course; and on his part Dr. Parsons had received word from some friend of mine, asking him to keep an eye out for me since we might be brought together at the Stockholm meetings. Neither form of introduction proved necessary. Dr. Parsons combined perfect courtesy with an ability to overcome diffidence, in a manner which equipped him admirably for the role which he played so well and which it is quite certain he greatly enjoyed, that of ambassador without portfolio. This was enhanced by the hospitality of his home, over which Lady Parsons presided with grace and warmth, and by the renown of the Children's Hospital, which largely by virtue of his stimulating participation supported an active and highly effective programme of clinical research. Over the years Sir Leonard succeeded in influencing, in helping, in uplifting an extraordinarily large number of people in widely separated areas of the world. My own debt to him is great indeed.

Dr. Parsons's keen interest in problems of growth and development must have guided in some measure the choice of subject which was assigned for these lectures. Indeed, the impetus which he gave to studies of the many-sided evolution of the individual through infancy, childhood and youth toward maturity reflects his appreciation that the effort to understand thoroughly the growing person calls upon every resource of the clinical art. In this conviction, as in many others, he was ahead of his time.

Growth is a conspicuous characteristic of the young of any species, so much so that one whose attention is occupied with infants and children finds it all too easy to take growth for granted. The natural expectation that a young person will continue to increase in stature and weight, and to advance at the same time in maturity, is fulfilled so often in the face of a variety of everyday vicissitudes that one too readily believes that growth will take

* The Leonard Parsons Lectures delivered in Birmingham on May 7 and 8, 1957.

care of itself. All that is required, however, to prick this complacent bubble is to ask oneself whether a given individual, an infant or a child, is growing as well as he can and as he should. Here we come squarely up against a formidable pair of questions, How does one determine optimal growth, and how can it be attained?

At the outset it must be admitted that we have no way of knowing what is best in the matter of growth. We can establish that one rate of growth is faster than another. Admitting the risk of a non-sequitur, we may even assert that a new achievement in growth, being demonstrably faster, is therefore better—an assumption one would find difficult indeed to prove. Even so, it is initially only too clear that in this quest of the absolute we cannot expect in any single step to close more than part of the gap which separates what we know to be attainable from that which we regard as perfection. Only in the course of infinite time can the best in growth be approached as a limit. And the closer we come to our goal, the more difficult it becomes to distinguish the results of our own manipulations from the operation of pure chance. The student of growth depends heavily on biostatistical method and on tests of significance to protect himself from false deductions.

The clinician, appreciating that in the immature animal growth is in some degree a measure of health, seeks a healthy population in which to attempt a quantitative definition of satisfactory or exemplary growth, and in doing so comes up at once against the related question, What is health?—or, specifically, Who is healthy? It is all very well for the World Health Organization to define health as something more positive than the absence of disease; but the identification of the truly healthy child in objective as well as positive terms becomes a formidable task unless one is willing to beg the question, come around full circle, and settle for the answer that he is a child who is growing properly.

Inferences and deductions based on studies of growth in experimental animals or in husbandry have, to be sure, limited direct application to the interpretation of growth in man. At the same time, they have served an important function in defining hypotheses which may then be put to the test in the study of infants and children, either by manipulation of the environment or by analysis of experiments of nature. It will be found that a great many aspects of the vast problem of nutrition in its relation to growth prove downright misleading when transferred from the experimental laboratory animal to man. Certain phases of the relationship of endocrine gland function to growth, although well defined so far as they apply to experimental animals, have yet to be confirmed in their application to human subjects. A conspicuous example which immediately comes to mind is the huge discrepancy between the experimental demonstration of the role of the pituitary growth hormone in the rat and the inconclusive evidence for a comparable role (at least with the currently available products) when efforts are made to accelerate the growth of a child afflicted with what we regard as hypophyseal dwarfism. In general, then, reliable data on growth in man are to be sought almost exclusively in the study of man.

Linear growth as a biological event has its basis in three fundamental phenomena: cell multiplication, increase in cell size and accumulation of extracellular material. Each of these processes in certain ideal circumstances follows a course which can be described by a relatively simple mathematical equation. Human growth, however, expressing the result of a variety of processes taking place simultaneously, is not easily pinned down in concise mathematical terms. The reasons are several: for one thing, differentiation of tissues begins not long after fertilization of the ovum, and single tissues grow at different rates; again, size and shape of the body are determined only in part by aggregates of cells, since a large and almost continuously variable contribution derives from inert products or accompaniments of cellular activity; and finally, the momentum of growth in the individual is subject to a variety of influences, the effects of which can be anticipated only imperfectly. As a result, the curve of growth as actually observed and recorded reflects the push and pull of a number of forces; and if it happens to coincide fairly well with the plot of an equation of growth or with a succession of such equations, this conformity ought perhaps to be looked on as something of a mathematical accident. One recoils instinctively from the notion that mathematical elegance in studies of human growth is to be purchased only at the price of repeated shifting of formulas as well as of parameters. Such faithless promiscuity indeed departs so far from elegance as to approach vulgarity. Medawar (1945), in one of the essays on growth presented in 1945 to D'Arcy Thompson, struck a proper balance between theory and empiricism in studies of growth when he wrote:

> 'Those who attach great importance to the concrete forms of growth equations are not as a rule put out when the whole course of growth has to be resolved into two or more separate periods or cycles, each to be described by special functions, or by a single function which abruptly changes the values of its parameters at what can here truly be

> called the psychological moment. . . . There is little in the development of the chicken to suggest that its life is really punctuated by these radical metamorphoses.'

What he said of the growth of the chick applies to man also.

The difficulty of formulating any universal mathematical law of human growth is pointed up by consideration of those studies which undertake to compare the growth of any one tissue or portion of the body with that of other segments or of the body as a whole. The fact that differential growth rates of individual tissues appear early and continue throughout foetal life has been well documented by Scammon (1930), by Clatworthy and Anderson (1944) and by others. Plots of the weight of individual foetal organs or parts, measured against foetal age, show little parallelism among the various curves. Similar studies of foetal stores of fat, protein, water and various mineral constituents (Widdowson and Spray, 1951) show comparable divergence. In healthy infants, Forbes and Perley (1951), Ely and Sutow (1952) and Friis-Hansen (1955) have employed a variety of devices for measuring the total water content of the body at different ages and have estimated both intra- and extracellular water in relation to postnatal age. Growth of the various fluid compartments of the body runs fairly parallel to that of length or weight. On the other hand, growth of total body fat follows a curve of its own. Throughout infancy and childhood girls tend to have more subcutaneous fat than do boys of like age (Kornfeld, 1957; Reynolds, 1950), a circumstance for which girls often have reason to be thankful when sea bathing is the popular sport. The diversity of growth trends and growth rates in such selected tissues as haematopoietic marrow (Osgood, 1955), fingernails (Babcock, 1955), pituitary fossa (Acheson, 1954a), head width (Meredith, 1953) and long bones of upper and lower extremities (Maresh, 1955) sounds a warning that each aspect of growth deserves individual study if experience is to have predictive value.

From clinical observations, from the studies of anthropologists, from experiments in biological laboratories or from knowledge of the facts of life as seen on the farm, one can readily assemble a list of factors which are known to influence growth and development or which are suspected of having such an influence. The measurement of these influences, their evaluation in quantitative terms, is of practical significance to clinical medicine. At the same time, the task is one of formidable difficulty in view of the large number of variables which operate simultaneously.

Without attempting at the moment to assign relative values to any of these factors which are known or believed to affect growth, it may be of some use to list them in rather general terms in order to have them in mind for later comment. On a broad scale they can be divided into three groups : (1) Factors which are genetically transmitted; (2) circumstances of the external environment; and (3) conditions of the internal environment. Concerning each one, and indeed concerning subdivisions of each, either there has been evidence advanced indicating an effect on growth, the magnitude of which only remains to be more precisely measured, or there has been fruitful speculation leading at times to the collection of convincing data.

Taking growth determinants in the order in which I have just given them, I must comment first on genetic influences. Phenotypic sex is genetically determined, by and large, save for the few interesting exceptions which have come to light in recent years as a result of applying Barr's methods (1956) to the identification of genotypic sex according to nuclear chromatin pattern. For the most part sex runs true to form, so to speak, being determined by the chromosomal equipment of the particular spermatozoon which fertilized the ovum, whether it contained the X or the Y chromosome. Sex differences in growth rate appear even before birth, male foetuses being heavier and females being more advanced in bone maturation. These sex differences become quite pronounced somewhere around the sixth to eighth year when in many girls the prepubertal spurt begins to make itself known. The earlier onset of the pubertal growth acceleration in girls as compared with boys, and its earlier termination, are well documented phenomena. The greater deposition of subcutaneous fat in girls has already been mentioned. Sex differences are recognized, and there is no risk of their being lost from sight.

Concerning the effect of race, ethnic group, or whatever might be thought of as the human equivalent of what we call breed in domestic animals, it has proved difficult indeed to assemble unequivocal data. The necessary balancing of environmental factors such as food supply, disease experience and general living conditions has been omitted when measurements have been made of a circumscribed population living in its natural surroundings; and when through migration environments have been equalized, or nearly so, inter-marriage over the course of years has almost invariably beclouded genetic interpretations. Many studies of growth carried out over the past half century begin hopefully with the statement that the group of children

studied was selected from families of 'north European stock'. And what, exactly, does that signify in genetic terms? Indeed, in a number of careful growth surveys carried out in the United States (Meredith, 1941, 1951a, 1951b), where the difficulties of defining and interpreting so-called racial traits are as formidable as they are likely to be in any part of the world, the conclusion was reached that differences in mean stature and mean body weight found between contrasted population groups could not be proved to be due to racial, rather than environmental, differences.

Genetically transmitted traits other than racial characteristics may influence growth in other respects. Tall families and short families frequently run true to form—so true, in fact, that the appearance of a deviant of merely average stature will often set unthinking tongues to wagging. Retardation of growth associated with an inherited metabolic defect such as galactosaemia or the hepatic form of glycogen storage disease is well recognized. What is less clear is the extent to which subclinical deviations in functional performance may modify growth capacity. The need for additional study along these lines is obvious, and no student of the problem underrates its difficulty.

Among pertinent factors of the external environment, the first item I have listed is nutrition. In recent years the number of publications describing the impact of dietary factors on human growth has shown a decrease which marks a shift of the focus of interest. Alterations in the growth of children dependent on war or on widespread economic depression are closely correlated with the intensity of the fiscal disturbance, have been well documented, and call for political and social adjustment rather than for special attention from the medical profession (Howe and Schiller, 1952). Of more direct concern to students of physiology are the efforts aimed from time to time at rendering an adequate diet even better by addition of an essential substance which is believed to be present in marginal quantity. For example, claims have been made for a growth-accelerating effect of supplementation of a conventional diet with small increments of vitamin B_{12} (Larcomb, Perry and Peterman, 1954). In view of the small numbers included in the study, and the probability that differences in stage of maturation at the particular age level of the test subjects complicated the problem of sampling, the conclusions expressed by the authors may well be interpreted with some caution. Comparable scepticism must be applied to claims voiced by Mülhausen (1953) for Goetsch's T-vitamin. In this connexion mention should be made of the demonstration by Baptist and de Mel (1955) that Ceylonese children reared on a cereal-legume-vegetable diet grew as satisfactorily as did a test group for whom a supplement of milk protein was provided. Their subjects were between 1 and 6 years of age. Earlier reports of similar studies carried out by Dean (1951) and Dean and Schwartz (1954) both in Germany and in Uganda seem somewhat more candid in recognizing the technical difficulties encountered.

The superiority of an adequate diet over an inadequate one is perhaps less subtly measured in terms of growth than by other criteria, particularly biochemical criteria, which can define the inadequacy more accurately than is feasible by conventional measures of external dimensions.

Macy, whose long experience in meticulous studies of nutrition endows her judgments with unusual claim to respect, has tilted a lance against the instinctivists and has asserted that appetite in children is not to be trusted to assure appropriate growth even in the presence of ample food and in the absence of known infection or other disease. In a series of experiments published in 1951 in association with Hunscher she came to the conclusion that for some subjects the voluntary intakes of food were not providing sufficient calories for satisfactory weight gains; and she stated that 'neither appetite nor any of the known standards can be relied upon to provide adequate food intakes for individual children' (Macy and Hunscher, 1951). In view of the fact that most of her subjects were between 5 and 10 years old and therefore at a highly impressionable age, one cannot refrain from wondering whether any of them were unhappy in the conditions of the experiments. Against these more modern studies may one not cite the observations of Clara Davis (1928) published long ago which led her to exactly the opposite conclusion, namely, that infants and young children who were permitted to select their own diet, qualitatively and quantitatively, from both variety and abundance set before them surpassed in their growth over a year or more the accepted normal standards of those times. Widdowson's observations (1951) in German orphanages showed convincingly that a child's affective reaction to supervisory personnel clearly influenced his weight gain, overbalancing the effect of minor differences in caloric intake. A comparable response in statural growth, although less prominent, was none the less detectable.

The suspicion that geographical location affects growth rates seems implicit in many careful studies of the problem. The device of sending a convalescent off to some remote region for a change of

climate in the interests of his health is firmly established in clinical thinking and practice. A comparable approach to the growth question sounds distinctly plausible. Yet as a thesis it is obstinately resistant to rigorous proof. For some years in the United States there lurked the suggestion that the growth rates found in studies made in communities of the Middle West and the Far West, more rapid than those recorded from cities of the Atlantic seaboard, supported the advice which Horace Greeley had given so often and so emphatically a century ago: 'Go west, young man.' One rather expected a Texan or a Californian to endorse the notion that out in God's country people naturally grew bigger as well as better. But in these comparisons longitude was not the only variable. True enough, when it became apparent that Boston children of 1879 or New York children of 1899 were being matched age for age with groups from other areas, geographic location appeared to exert less influence than did the so-called secular trend, the gradual acceleration of growth over several decades. Meredith, one of the most careful and critical students of growth, reviewed the entire subject in 1941, so far as American data were concerned, and came to the conclusion that no clear difference could be established between the growth rates of children reared in urban as contrasted with rural surroundings, nor between rates from different pairs of urban communities chosen from widely separated and representative parts of the country. More recently Newcomer and Meredith (1951) published observations made on a 1950 sample of 15-year-old boys from Eugene, Oregon, in which the means for both weight and height exceeded those of any other recorded community; but the samples were small, and with the caution that comes of long experience they slyly refrained from expressing an opinion regarding their significance, so far as the geographical factor was concerned.

Variations in growth rates with season of the year have been recorded fairly frequently (Palmer, 1933; Reynolds and Sontag, 1945). In studies carried out in Maryland, gain in weight per calendar month reached a peak in the month of October. Seasonal acceleration of growth in height is more subtle and considerably more difficult to demonstrate. It seems impossible to determine with available evidence whether such fluctuations depend directly on the solar cycle, responding to the influence of daylight, sunshine, environmental temperature, and such; or whether they are indirectly related to the solar angle and reflect the influence of changes in diet, in school demands, in vacation mood. In at least one study from the southern hemisphere, that of Fitt (1924), the peaks and dips in the curve of weight gain are in reciprocal phase, showing maxima in April, May and June and minima in October, November and December.

Great interest continues to be focused on evaluation of the secular trend, the acceleration of growth and maturation which children of today exhibit in comparison with similarly selected children of past generations. Of the phenomenon itself, the greater height, weight, and other measurements, of children of a given age when matched against the records of children of the same age in their fathers' time or earlier, no serious doubt persists. Whether adult height is likewise increasing with time remains somewhat in dispute, and adult weight has too little finality about it to deserve elaborate statistical analysis. But in respect to stature, even if one concedes for purposes of argument that today's adults are no taller than their forebears, the secular trend in the growth of children is reflected in a progressive shifting to the left of growth curves on the time scale (Meredith, 1941 ; Weir, 1952 ; Clements, 1953). Clements (1953) summarizes the trend over a 70-year interval by showing that in height and weight the 6-year-old of 1953 is at about the same stage as the 7½-year-old of 1883. A variety of explanations have been offered. Berry and Cowin (1954) point out that the increase in growth rate is accompanied by slimmer physique. Bennholdt-Thomsen (1942) postulated selective breeding and selective survival of taller, more slender types, and this position has been staunchly supported by Freund and Maier (1952), though one is hard put to it to understand how these ordinarily slow-moving forces can produce in so short a space of time the results actually found. Most students of the secular trend have regarded it as the net expression of a variety of forces including availability of food, understanding of nutrition, relative freedom from significant infectious disease, purchasing power of family units, housing, public sanitation. Nevertheless, the paradox remains that as each single item is individually tested for significance by as careful matching of samples as the data and changing conditions of the times permit, as Meredith (1951a), Weir (1952), Clements (1953) and others have done, a large fraction of growth acceleration remains unexplained. Dissection of the secular trend is, as Meredith (1951a) and Morant (1951) in particular have emphasized, a promising assignment for future studies.

Evaluation of the internal environment in its bearing on growth and development amounts almost to a paraphrasing of the paediatrician's clinical responsibility to his patient. Simply for the purpose

of establishing broad subdivisions I have listed four spacious territories where the hunting is apt to be rewarding, namely, the regions of (1) disturbances of utilization of structural material, (2) endocrine imbalance, (3) malformations of one sort or another, and (4) infections of all kinds. There is little point in attempting to survey in detail the entire area in which the search for causes of disturbed growth must be made, for it is all familiar territory to clinicians and has been well set out in a number of textbooks in common use. A word may be said, however, about trends in the study of specific problems of growth.

Without much question styles in clinical investigation have changed over the past few years; new ideas and a new freedom have been introduced, and the accuracy of identification of causes has increased impressively. Emphasis has shifted from concern over the minutiae of the diet to a more careful appraisal of the patient himself. The trend in feeding practices toward encouraging a child to be omnivorous from an early age has amply demonstrated that excellent growth may be attained with a quite wide variety of menus. A deficient diet can still account for slow growth, but this is seldom encountered nowadays in your country or in mine save when ignorance and superstition have combined with economic restrictions to limit the child's freedom of selection. And with the shifting of focus to the patient and the increasing application of modern diagnostic aids, new causes emerge as the agents responsible for retarded growth: specific enzyme deficiencies such as galactosaemia or hepatic glycogen storage disease; the endocrine imbalance which accompanies the fundamental gonadal disturbance in Turner's syndrome; coarctation of the aorta, pancreatic fibrosis, a variety of anomalies of the kidney; and such vaguely localized functional curiosities as the severe form of idiopathic hypercalcaemia (Schlesinger, Butler and Black, 1956). The only purpose of this fragmentary enumeration is to emphasize the point that over a relatively short space of time such as the past 20 years, means have not only been found but also popularized and made widely available for the accurate identification of responsible factors in problems of growth and development. Save for the reflection that perhaps the richest ores have already been mined and that those who come after may have to dig deeper and employ more elaborate refining processes, there is no reason to anticipate an important slacking off of progress in finding explanations. Finding remedies is, of course, another matter.

Thus far I have chosen to rehearse in summary fashion and in general terms some of the factors which influence growth—linear growth, increase in weight—without giving due attention to maturation or development. All of the causative agencies just referred to exert an analogous effect on maturation, usually in the same direction or with the same sign.

Maturity has been defined as the state of complete natural development, and degree of maturation may be looked on as a station along the way. Let us first consider skeletal maturation. The task of evaluating it is usually handed over to the radiologist, who studies whatever radiographs he considers appropriate—the hand and wrist, perhaps a knee or foot, or even one-half of the skeleton—and, taking account of the patient's sex, reports back that skeletal maturation is within normal limits for a boy or girl of stated age, or perhaps is abnormal. In the latter event, if the skeletal maturation is alleged to be retarded, or if it is advanced, the question of degree is certain to come up.

Several methods are in common use for evaluating skeletal maturation. In one, films of the patient's hand and wrist are compared with standards contained in an atlas, perhaps Todd's original atlas (1937), or the later modification published by Greulich and Pyle (1950). With either standard of reference, the patient's film is graded as being equivalent to a certain bone age for the corresponding sex. Todd himself had apparently expected two assessors of unequal experience to rate maturation within about six months in a given case. Those who have used his atlas subsequently have often appeared to be somewhat more confident of their ability to pinpoint a maturational rating. In recent studies (Dreizen, Snodgrasse, Webb-Peploe, Parker and Spies, 1957) made on white children living in Alabama, it was found that when the two hands were compared, the skeletal age of the right hand exceeded that of the left hand in 52%, was equal in 26%, and was less than that of the left hand in 22%. The greatest disparity was found in the epiphysis of the radius where the two sides got an equal rating in only 22% of the cases. In respect to individual centres in the carpus, the two wrists of a given individual might justify a reading differing by as much as 12 months' bone age or even more.

Mainland (1953, 1954) carried out an important study of both the systematic errors and the variable errors inherent in the method of estimating skeletal maturation by comparison of the patient's radiograph with a standard atlas. Pressing his wife into service as an assessor without previous experience, and therefore presumably without prejudice, he persuaded her to evaluate bone age in several films of the hand, the only information furnished being the sex of the subject. After an interval of several

months, the same films were reassessed in a different sequence. She then compared her readings with those which had previously been made by Todd and his collaborators on these identical radiographs. Later, she repeated the same procedure using the Greulich and Pyle atlas. On the whole, she tended to read skeletal ages lower than did the experts. Her systematic error was quite variable. The conclusion was drawn that the method was better adapted to determination of the average skeletal age of a group of children than to the assessment of bone maturation of an individual child, especially from a single film. The variable error was calculated from the scores made by the same assessor on different occasions, sufficiently separated in time so that memory would play no part. The irregular variation found between independent readings of the same film amounted to a standard deviation of three or four months. This means that, depending upon the age of the subject, the assessor would have to attach an error of ± 8 to 11 months to his estimate of skeletal maturation in order to achieve 95% significance. In other words, one must not look for greater accuracy than the method itself admits; and perhaps some caution is warranted before one accepts a maturation rating at its face value.

Another method consists in the counting of centres of ossification in one-half of the body, a technique popularized by Elgenmark (1946) and by Harding (1952). Essentially it is an extension of earlier techniques in which centres were counted only in the hands and feet. The method has the great advantage of objectivity in scoring, since the presence of a calcified centre, rather than its pattern, constitutes the basis of evaluation. In common with the atlas method, this one has the advantage of making it relatively easy to state whether a given patient's bone maturation is accelerated or retarded, but the disadvantage of making it difficult to express this deviation in maturational units.

The list of procedures for evaluating skeletal maturation could be extended if there were much point in doing so. The large number of different techniques advocated and in use indicates that none has been found wholly satisfactory—an all too common situation in clinical therapeutics. I am well aware that this question has enlisted the interest of Acheson (1954b) and his group (Acheson, Kemp and Parfit, 1955) at the Social Medicine Unit of Oxford University, and it is to be hoped that their exploitation of the system of scoring by 'Oxford maturity units' will overcome the difficulties experienced with other methods of assessment. By scoring both hands for each evaluation they do indeed avoid the irregularity which results from chance inequalities of bone pattern in the two hands. Careful as they have been in the timing of the ages of their subjects who have served to set the pattern, it is not yet entirely clear whether the increment in maturity from, say, 5 to 6 maturity units, is equivalent to the increment from 20 to 21 units. In other words, has linearity been fully established? Another practical difficulty, soon to be resolved no doubt, is that thus far the published standards extend only up to age 6 years. But the basic principle of scoring maturation in maturity units or in fractions of ultimate maturity, and not in time units, represents a distinct advance over the older and more prevalent device of registering bone maturation in terms of so-called bone age.

Other means of estimating maturation are available besides the pattern of bones as seen in radiographs. The eruption and exfoliation of teeth follow trends which enable one to estimate so-called dental age objectively and quite accurately. The bodily changes which mark the process of sexual maturation normally follow fairly well defined sequences and lend themselves to semi-quantitative evaluation. Likewise, patterns of neuromuscular behaviour and of intellectual attainment ordinarily show a correlation with chronological age which provides a useful tool in the assessment of an individual child's functional capabilities, if one is looking ahead, or of his achievements in neural organization and mental growth, if one is more interested in measurement of past attainment. Independent evaluation of these several functions is of enormous value in the diagnosis of endocrine disturbances like hypothyroidism, and in the titration of results of replacement therapy. Indeed, every well organized endocrine clinic relies heavily on a battery of tests of maturation in following examples of retarded or accelerated growth and development of all sorts, for it is in these endocrine clinics where, rightly or wrongly, such patients usually land. Every clinical investigator who has probed deeply into problems of disturbed growth and development (Prader and Perabo, 1952; Talbot, Sobel, McArthur and Crawford, 1952; Wilkins, 1950) has focused due attention on what might be called differential maturation. Perhaps the odd feature of current practices in this regard is the limited number of fields which the clinician concerned with problems of growth has been willing to cultivate intensively. It seems probable that future efforts will devote more attention than is now customary to the wide variety of functional aspects of development which invite exploration, as contrasted with the rather limited anatomical territory

in which the search for measurable components now tends to operate.

Careful studies of the complex processes of puberty and adolescence, of which a number have been organized in the past few decades, have thrown fresh light on growth and development from several points of view. It has become clear, for one thing, that a secular trend in earlier sexual maturation of girls is discernible over broad spans of time such as 50 or 100 years (Brock, 1954). A comparable acceleration in sexual maturation of boys, although less firmly substantiated, is nevertheless highly probable. With earlier maturation goes earlier appearance of the prepubertal growth spurt; and while this precession of the normal childhood acceleration of linear increase is readily demonstrable in the average behaviour of large populations, its effects are most conspicuous when measured in the individual child. Earlier onset of the growth spurt goes hand in hand with earlier attainment of maximal rate and also with earlier attainment of the limit of linear growth. In other words, the secular trend shows both boys and girls reaching mature height at a younger age : for boys, according to Clements (1954), at age 17 years 9 months on the average, with a standard deviation of close to 10 months ; for girls, at a mean age of about 16 years 3 months with a standard deviation of 13·6 months. Evaluation of skeletal maturation with relation to age and attained height has permitted certain students of growth problems (Bayley, 1956; Bayley and Pinneau, 1952; Tanner, 1955) to predict ultimate height with greater accuracy than would be possible on the basis of age and height alone. In the management of problems of endocrine imbalance associated with dwarfism, maturational aspects of development are accorded fully as much attention in the assessment of treatment as are the simple linear aspects of growth. These considerations have become all the more important since pharmacological agents now available have sufficient potency to accelerate skeletal maturation to a harmful degree in that, by speeding up the process, they can actually cause fusion of epiphyses, and therefore cessation of growth, before the patient's inherent growth potential has been realized.

Now, although most of the factors which influence growth have been touched only lightly and many have not been mentioned at all, it is appropriate to return to the basic clinical situation, the physician confronted with a patient, a growing patient. With respect to the patient's growth status the physician formulates a hypothesis which takes one of three forms : (1) Up to now the child has grown adequately; or (2) his growth has been insufficient; or (3) it appears to have been excessive. The hypothesis is now to be tested by measurement of the patient and matching his measurements against some standard of reference. Most doctors have messed around sufficiently with tape measures, scales and clocks to understand the technique of mensuration and to know when and how mistakes are commonly made. They realize that every measurement involves an error of mensuration, and they understand fairly well that when two comparable measurements are added together, the error of the sum is somewhere between the smaller of the two individual errors and twice the larger of the two. I suspect it is not so clearly appreciated that when one measurement is divided by another, in order to obtain a ratio, the error of the quotient may be very much greater than the error of the sum. This risk of self-deception applies to such apparently innocent procedures as obtaining a cardiothoracic index, or the ratio of the linear measurements crown-to-pubis over pubis-to-heel.

At this early stage of evaluation, in the first-order testing of the three simple, basic hypotheses just mentioned, what dimensions need to be measured? Is it enough to weigh the patient and to record a single linear index such as standing height or recumbent length? Or should one follow the lead of the students of growth and include sitting height, span, head width, head circumference, shoulder width, intercristal diameter, intertrochanteric diameter, thickness of subcutaneous tissues, and so on? Practices do indeed vary widely. On the whole, I would defend the simplest sort of evaluation at this stage, leaving until later the more meticulous and detailed measurement in the event that examination did actually bring out evidence of growth disturbance. Every physical examination of an infant or child should comprise a sort of battery of assessments—of body build, organ size, dental maturation, neuromuscular development, even in a rough way mental competence, all with relation to attained age. Any unusual findings turning up in the course of a thorough clinical evaluation will then point the way toward those specific dimensions which one will later want to watch with particular care. As I review my own sins of omission I have no inclination to regret that I have refrained from subjecting hospital and clinic patients to detailed routine measurements merely for the sake of accumulating data, but I do wish that some of the time thus saved had been devoted to a more detailed exploration of the course of growth in those patients whose clinical problem was found to include impairment or acceleration of growth.

What standard of reference is now to be used in judging the adequacy of growth? Ideally, of course, the frame of reference for the individual patient ought to be a healthy population of his own general group. In most situations no such standard is available, and the clinician must then ask himself how much difference it makes in actual practice to refer to whatever growth tables are at hand. If the inquiring physician happens to be over-conscientious and consults more than one set of tables, he is almost certain to find divergent answers and to become progressively more confused and unhappy the farther he searches. At this stage of the assessment of a clinical problem it seems to me to make little difference whether the frame of reference used is new or somewhat less than new, provided it has been so designed as to afford a convenient way of estimating, either through calculated percentiles or through multiples of the standard deviation, the degree to which the patient under scrutiny varies from the given mean for his age and sex. Tanner (1952) has put the problem in proper perspective by pointing out that one's criteria for separating normal from abnormal depend largely on what is planned as the next step : if the next step is to be closer study of the patient, then one will be far more willing to classify a measurement as abnormal than if the decision is tantamount to relegating the patient to some corner of limbo. In this respect it is a fortunate accident of history that in growth matters the standards of reference, the available tables of height and weight for age and sex, have usually lagged some years behind the uses to which they are put; and in view of the secular trend toward acceleration, the net effect has been to provide a somewhat spurious satisfaction with modest achievement. When the practical outcome of the evaluation of new measurements by old criteria has been to allay suspicion in respect to marginally retarded growth, the resulting tranquillity has no doubt been all to the good, so long as really pressing problems are not entirely overlooked. And on the other side of the coin, no great harm is done when the practitioner pats himself on the back because the great majority of patients under his care are above average in their growth attainment, again by comparison with outdated standards of reference.

Once it has been admitted that the individual child presents a problem in growth, because his achievement thus far leaves something to be desired, the next questions, How fast is he growing, and Will his rate of growth enable him to close the gap eventually? are of a quite different order of technical complexity. Students of growth (Meredith and Meredith, 1950 ; Shuttleworth, 1951 ; Tanner, 1952) extol the study of growth rates and point out how much more is to be learned from a knowledge of the speed of growth at a given age than from the mere attainment of length or whatever other dimension in relation to chronological age. At the same time it must be kept in mind that with inaccurately measured linear dimensions separated by too short a time interval the error of measurement can easily lead to absurdity. While I am quite prepared to agree that the most accurate evaluations of growth progress are attainable through careful determinations of rate in relation to stage of maturation, it is perhaps permissible to express a word of caution to the clinician who might be tempted to approach this assignment lightly.

Rate of growth in relation to stage of maturation —this is really the gist of the problem of assessment of the individual. It sounds easy, actually it is difficult, and yet even with all its possible sources of error it can be rewarding in its prediction of later performance. The accuracy with which chronological age can be measured, to four, five, or even six significant figures, must not be allowed to lure us into excessive faith in the value of the time dimension when we are trying to learn whether the patient before us has a favourable chance of growing into a pleasing and effective adult. At any given age the range of acceptable variation about a mean value may be quite large—more for some dimensions than for others. For boys 3 years of age, for example, the coefficient of variation $\left(\frac{100\ \text{S.D.}}{\text{Mean}}\right)$ for height is of the order of 3, for weight of the order of 10 (Thomson, 1956), and for skeletal maturation by the Elgenmark technique of the order of 30. The paradox is that in our actual evaluation of the patient, especially if he shows evidence of endocrine imbalance, our predictions and sometimes our diagnostic judgments rely fully as much on our estimate of maturation, the most variable of the dimensions measured, as on any of the other parameters. Again, one must plead for more intensive study of all aspects of maturation in order that our tools of measurement may be brought to ever finer calibration. In the assessment of the problems of adolescents, in whom the vagaries of sexual maturation are closely bound up with emotional adjustments as well as with simple physical growth, we have to recognize that much remains to be accomplished. In spite of the meticulous studies of Bryan and Greenberg (1952), of Hogben, Waterhouse and Hogben (1948), of Shuttleworth (1951) and others, it would seem premature to claim that the measurement of sexual maturation has been put on an altogether satisfactory quantitative basis.

Growth and development encompass too large an area to permit one to summarize the current state of our information with any sense of contentment. In a condensation such as I have attempted, omissions are unavoidable, and distortions are certain to intrude. I have tried to bring to the fore those features which seem to me of relative significance in the clinical evaluation of a patient's status and prospects—in his anatomical assessment at a time when he is still short of full maturity. In the course of the past several years improvements have been made in the techniques of measurement, though most of these are not of major importance. A more significant advance lies in greater acceptance of the range of expected variation consistent with health, in willingness to consider a variety of possible causes when growth disturbance is recognized, and, finally, in appreciation that the patient himself deserves intensive study as well as his background and his environment.

REFERENCES

Acheson, R. M. (1954a). *Brit. J. Radiol.*, **27**, 298.
—— (1954b). *J. Anat. (Lond.)*, **88**, 498.
——, Kemp, F. H. and Parfit, J. (1955). *Lancet*, **1**, 691.
Babcock, M. J. (1955). *J. Nutr.*, **55**, 323.
Baptist, N. G. and de Mel, B. V. (1955). *Brit. J. Nutr.*, **9**, 156.
Barr, M. L. (1956). *Canad. med. Ass. J.*, **74**, 419.
Bayley, N. (1956). *J. Pediat.*, **48**, 187.
—— and Pinneau, S. R. (1952). *Ibid.*, **40**, 423.
Bennholdt-Thomsen, C. (1942). *Ergebn. inn. Med. Kinderheilk*, **62**, 1153.
Berry, W. T. C. and Cowin, P. J. (1954). *Brit. med. J.*, **1**, 847.
Brock, J. (1954). *Biologische Daten für den Kinderarzt*, 2nd ed., Vol. 1, p. 86. Berlin.
Bryan, A. H. and Greenberg, B. G. (1952). *Hum. Biol.*, **24**, 117.
Clatworthy, H. W., Jr. and Anderson, R. G. (1944). *Amer. J. Dis. Child.*, **67**, 167.
Clements, E. M. B. (1953). *Brit. med. J.*, **2**, 897.
—— (1954). *Archives of Disease in Childhood*, **29**, 147.
Davis, C. M. (1928). *Amer. J. Dis. Child.*, **36**, 651.
Dean, R. F. A. (1951). *Brit. J. Nutr.*, **5**, 269.
—— and Schwartz, R. (1954). *Courrier*, **4**, 293.
Dreizen, S., Snodgrasse, R. M., Webb-Peploe, H., Parker, G. S. and Spies, T. D. (1957). *A.M.A. J. Dis. Child.*, **93**, 122.
Elgenmark, O. (1946). *Acta paediat. (Uppsala)*, **33**, Suppl. 1.
Ely, R. S. and Sutow, W. W. (1952). *Pediatrics*, **10**, 115.
Fitt, A. B. (1924). *Rep. Aust. Ass. Adv. Sci.*, **16**, 704.
Forbes, G. B. and Perley, A. (1951). *J. clin. Invest.*, **30**, 558.
Freund, J. and Maier, E. H. (1952). *Z. Kinderheilk.*, **71**, 1, 79.
Friis-Hansen, B. (1955). *Helv. paediat. Acta*, **10**, 12.
Greulich, W. W. and Pyle, S. I. (1950). *Radiographic Atlas of Skeletal Development of the Hand and Wrist.* Stanford University Press.
Harding, V. S. V. (1952). *Child Developm.*, **23**, 247.
Hogben, H., Waterhouse, J. A. H. and Hogben, L. (1948). *Brit. J. soc. Med.*, **2**, 29.
Howe, P. E. and Schiller, M. (1952). *J. appl. Physiol.*, **5**, 51.
Kornfeld, W. (1957). *Hum. Biol.*, **29**, 62.
Larcomb, J. W., Perry, C. S. and Peterman, R. A. (1954). *J. Pediat.*, **45**, 70.
Macy, I. G. and Hunscher, H. A. (1951). *J. Nutr.*, **45**, 189.
Mainland, D. (1953). *Pediatrics*, **12**, 114.
—— (1954). *Ibid.*, **13**, 165.
Maresh, M. M. (1955). *A.M.A. J. Dis. Child.*, **89**, 725.
Medawar, P. B. (1945). In *Essays on Growth and Form, presented to D'Arcy W. Thompson*, ed. Clark, W. E. Le Gros and Medawar, P. B., p. 157. Oxford.
Meredith, H. V. (1941). *Amer. J. Dis. Child.*, **62**, 909.
—— (1951a) *A.M.A. J. Dis. Child.*, **82**, 702.
—— (1951b). *Growth*, **15**, 39.
—— (1953). *Pediatrics*, **12**, 411.
—— and Meredith, E. M. (1950). *Child Developm.*, **21**, 141.
Morant, G. M. (1951). *Brit. med. Bull.*, **7**, 316.
Mülhausen, W. (1953). *Mschr. Kinderheilk.*, **101**, 13.
Newcomer, E. O. and Meredith, H. V. (1951). *Hum. Biol.*, **23**, 24.
Osgood, E. E. (1955). *Pediatrics*, **15**, 733.
Palmer, C. E. (1933). *Publ. Hlth Rep. (Wash.)*, **48**, 211.
Prader, A. and Perabo, F. (1952). *Helv. paediat. Acta*, **7**, 517.
Reynolds, E. L. (1950). *Monogr. Soc. Res. Child. Dev.*, **15**, No. 2. Child Development Publications.
—— and Sontag, L. W. (1945). *J. Pediat.*, **26**, 336.
Scammon, R. E. (1930). In *The Measurement of Man*, by Harris, J. A., Jackson, C. M., Paterson, D. G. and Scammon, R. E., p. 173. Univ. of Minnesota.
Schlesinger, B. E., Butler, N. R. and Black, J. A. (1956). *Brit. med. J.*, **1**, 127.
Shuttleworth, F. K. (1951). *Monogr. Soc. Res. Child. Dev.*, **14**, Nos. 1, 2. [1949.]
Talbot, N. B., Sobel, E. H., McArthur, J. W. and Crawford, J. D. (1952). *Functional Endocrinology from Birth through Adolescence.* Harvard University Press.
Tanner, J. M.(1952). *Archives of Disease in Childhood*, **27**, 10.
—— (1955). *Growth at Adolescence.* Oxford.
Thomson, J. (1956). *Brit. J. prev. soc. Med.*, **10**, 128.
Todd, T. W. (1937). *Atlas of Skeletal Maturation.* St. Louis.
Weir, J. B. de V. (1952). *Brit. J. Nutr.*, **6**, 19.
Widdowson, E. M. (1951). *Lancet*, **1**, 1316.
—— and Spray, C. M. (1951). *Archives of Disease in Childhood*, **26**, 205.
Wilkins, L. (1950). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence.* Springfield, Illinois.

PART II. PHYSIOLOGICAL CONSIDERATIONS

Physiological maturation represents in some degree the process of adaptation to the new requirements of a changing environment.

Perhaps the first task of the infant at birth is to insure for himself a proper supply of oxygen in the shift from placental to pulmonary respiration. By and large, this adjustment is one which he achieves by his own efforts. What we can do for him remains rather tentative in spite of the vagaries of fashion with respect to techniques of what we are still pleased to call resuscitation.

Great uncertainty still surrounds the concept of what actually represents a proper oxygen supply for a newborn infant. There is good reason to believe that the oxygen requirement of the newborn infant is not by any means as immediately pressing as would be that of an older individual in comparable circumstances. Indeed, studies of postnatal oxygen saturation of arterial or capillary blood (Apgar, Girdany, McIntosh and Taylor, 1955) have disclosed a wide range of variation in the time required for individual infants to attain an arterial oxygen pressure believed to be necessary for transport of oxygen in adequate quantity to the tissues. Some of the newborn infants whose blood oxygen we followed at intervals over the course of the first three hours after delivery were still showing blood oxygen levels of less than 5 volumes per 100 ml. as late as 15 minutes after birth, and a few for even longer; yet in subsequent evaluation three to five

years later they exhibited no demonstrable residua of their earlier hypoxaemia. The battery of tests to which these subjects were exposed included a careful history to uncover any episodes which might be classed as seizures, a detailed neurological examination and formal psychometric evaluation by a modification of the Stanford-Binet test. On comparison with controls, the patients who in early infancy had been exposed to low blood oxygen pressures had progressed as satisfactorily as had their more briskly oxygenated fellows in the observational group. These somewhat reassuring results stand in sharp contrast to the prevalent tendency among neuropathologists to attribute a number of clinical syndromes, including cerebral lesions, to the action of postnatal anoxia (Wolf and Cowen, 1954), even when the historical evidence for anoxaemia is unimpressive. While the biochemical studies referred to have served to remove some of the blame from the long-suffering whipping boy, postnatal anoxaemia, too readily accused of responsibility for such sequelae as mental retardation, cerebral palsy, or epileptic seizures, the role of prenatal anoxia remains largely unexplored, unmeasured. Uncertainty in regard to the oxygen requirement of premature infants is even more formidable, for in this area of the special biochemistry of the immature subject we are still groping for fundamental information.

Tolerance of the foetal and newborn mammal for low oxygen pressures at the tissue level has long been established for experimental animals and seems to be related to an alternative capacity to derive energy from carbohydrate breakdown through a process of anaerobic glycolysis (Wilson, Reardon and Murayama, 1948). Evidence that the human foetus possesses this capacity for anaerobic glycolysis has only recently been obtained (Villee, 1957). How long such a capacity for biochemical legerdemain persists, how long after the infant's birth it constitutes an available resource, is not yet certain. While it lasts, it apparently purchases energy at the cost of accumulation of non-volatile metabolic breakdown products, especially lactic and pyruvic acids, which cannot be got rid of as rapidly as can carbon dioxide and water. One result is the temporary establishment in the newborn infant of a metabolic acidosis which is expressed in the plasma by depression of the *p*H and of the concentration of bicarbonate ions. For some time following birth many premature infants exhibit periodic breathing in room air but can be made to breathe regularly when placed in an oxygen-enriched atmosphere. Wilson and his colleagues (1948) interpreted this phenomenon as evidence that the premature infant is apt to be incapable of meeting his full oxygen requirements by breathing ordinary room air. Nowadays, on the other hand, such evidence which might make one wish to enrich the oxygen content of the atmosphere to which premature infants are exposed is heavily counterbalanced by the risk of inducing retrolental fibroplasia (Crosse and Evans, 1952). An interesting observation on the developmental aspects of susceptibility to retrolental fibroplasia is the demonstration that, when once the retinal vessels have grown far enough to reach the ora serrata, they are no longer readily vulnerable to high oxygen injury (Ashton, Ward and Serpell, 1954).

The role of foetal haemoglobin in determining the transient peculiarities of oxygen utilization of the newborn infant has not yet been fully elucidated. The blood of premature infants has been shown by Jonxis (1949) and by Cook, Brodie and Allen (1957) to contain relatively large proportions of foetal haemoglobin, averaging close to 90% of total haemoglobin, while the blood of mature newborn infants contains somewhat less, averaging about 72%. Although foetal haemoglobin is known to take up oxygen in the alveoli more readily than does adult haemoglobin, at the same time it gives up oxygen less readily to the tissues. The latter characteristic has been offered as a partial explanation of the relative anoxia of premature infants. Whilst the concentration of carbonic anhydrase in the newborn infant's blood is only about half that of the adult, and in the premature infant as little as one-quarter (Stevenson, 1943), there is no proof that these reduced quantities of the enzyme constitute a physiological handicap (Day and Du Pan, 1949). In other words, shortage of carbonic anhydrase cannot be offered as an explanation of inadequate pulmonary alveolar exchange of CO_2 for O_2. Save for the accurate mapping of the disappearance of foetal haemoglobin from the infant's blood with time and growth (Jonxis, 1949), most of the biochemical and physiological changes just described which have to do with oxygen supplies have not been fully exploited as maturational phenomena.

The infant's ability to regulate his body temperature is dependent in part on his state of maturity. With falling body temperature the point at which shivering begins is lower in the premature infant than in one born at term; some very small infants in fact fail to show reflex shivering at all. With rising body temperature the premature infant is again at a disadvantage in that his deficient sweat production (Day, Curtis and Kelly, 1943) deprives him of the ability to lose heat by evaporation of

water from the skin surface. His relative poverty in subcutaneous fat adds to his difficulties in that, lacking its insulating properties, his tissues as a whole have a relatively high thermal conductance. The smaller the subject, the higher is the ratio of surface area to body weight, a potentially important aspect of heat gain or loss by convection and conduction. The practical significance of relatively large surface area, however, in the maintenance of steady temperature must in point of fact be of secondary order, for it is common to observe a gradual stabilization of a premature infant's body temperature, showing as a decrease in the excursion from highest to lowest point in a 24-hour cycle, long before gain in weight has accounted for more than a minute drop in the ratio of surface area to mass.

Observations documenting the development of the functions just mentioned are fragmentary in comparison with studies of renal regulatory capacity in early life, most of which have been carried out in the past decade. Only a brief and quite inadequate summary can be offered in this context. The ingenious investigations of McCance and Widdowson (1953) throw light on renal performance before birth as well as afterward. Urine collected from infants at the moment of birth, and therefore formed some time before, was compared with maternal urine and with urine excreted later by the infant. Prenatal urine was characterized by low osmolarity, less than half that of the cord serum, to which NaCl contributed a relatively large fraction and urea a small fraction; it usually contained a little more Na than Cl, comparatively little K, and only traces of inorganic P. These findings provoke interesting speculation as to the source of excess water over and above foetal growth requirements, and one must wonder also whether the foetal kidney is capable of responding to the antidiuretic hormone of posterior pituitary or to parathyroid hormone.

In order to explore the transition from intra-uterine to extra-uterine life, McCance and Widdowson (1954) then studied the urine excreted in the first two days of life by infants who during this period were given no food and little water, in all, only about 25 ml. of water over the course of 48 hours. In these circumstances the substances presenting for renal excretion are almost exclusively those which the infant brings with him into the extra-uterine environment or produces in the course of his own energy release. Although the volume of urine passed was small, as would be expected with essentially no intake of fluid, its osmolar concentration rose only moderately from the relatively low level of solutes found in prenatally formed urine. Indeed, its average osmolar concentration during the first two days after birth was only about one-third that which would be attained in the urine of adult subjects in comparable conditions of fasting and thirsting. Both urea clearance and glomerular filtration rates were at this stage low in comparison with values which one might expect of an older subject in relation to the volume of body water.

These and other findings may be looked on as manifestations of relative immaturity of renal function in the immediately postnatal period and in the first few weeks of extra-uterine life. Impressive ingenuity has been expended by a number of investigators (Rubin, Bruck and Rapoport, 1949; Vesterdal and Tudvad, 1949; McCance, 1950; Barnett, Vesterdal, McNamara and Lauson, 1952; McCance, Naylor and Widdowson, 1954) in defining with ever greater precision the quantitative aspects of this feature of physiological maturation. In view of the variety of methods used, substances measured and conditions of experiment, the coincidence of results and the agreement in interpretations appear little short of remarkable. Whether glomerular filtration rate is estimated by clearance of endogenous creatinine, mannitol, or inulin, all workers concede that immediately after birth the rate is relatively low, that it begins to rise almost at once, and that in the course of several days or weeks, possibly as long as a few months, it reaches values corresponding to those found in older subjects. The performance of the infant's kidney, if it is to be compared with that of an older, larger, and more mature person, must be brought into some common frame of reference such as weight, height or surface area. By general agreement all earlier workers evaluated their results after calculating equivalence with a subject benevolently endowed with the arbitrary standard surface area of 1·73 square metres. McCance and his colleagues (1954) introduced the device of referring urine flow and other renal functions to total body water, rather than to surface area. Although this calculation involves certain assumptions which may not be strictly valid for the individual infant, it does strive to relate renal performance to a bodily dimension more closely identified with what one expects of the kidney than is surface area. We do ask the kidney to maintain homeostasis with respect to water and electrolytes and other dissolved substances occupying the fluid compartments of the internal environment, and body water seems to be the kidney's direct business. Application of these calculations has the effect of bringing the infant's glomerular filtration rate close to the adult level at a much earlier age, within a month after birth, for instance, rather than in four months to a year as some earlier

estimates suggested. The use of calculated total body water as a frame of reference for evaluating renal functional maturation is not necessarily justified because it appears to accelerate adjustment to the circumstances of extra-uterine existence. Indeed, the possibility of an even more satisfactory criterion being exposed by closer study of the problem cannot be excluded from our speculations.

Another feature of renal function, clearance of those particular substances like para-aminohippurate and diodrast ('diodone') which are dealt with primarily in the tubules, is likewise found to be relatively low at birth, increasing with age but at a slower rate than the spontaneous rise in glomerular filtration rate previously mentioned. One practical result of relative immaturity of the young infant's kidney is his sluggishness in excreting certain substances used in treatment of infections, like penicillin, which leave the body chiefly by tubular excretion. It thus is easier with small infants to sustain a given plasma concentration of penicillin with doses usually used in therapy.

The ability of young infants to excrete a large dose of water administered by stomach tube has been studied by McCance *et al.* (1954). Again it becomes difficult to know precisely how to put small infants on the same footing as the adults with whom they are to be compared ; but when subjects of any age were given over a brief interval a dose of water amounting to 5% of their body weight, its excretion was appreciably less efficient on the part of infants younger than 3 weeks of age. Whereas an adult could regularly excrete 90% of the administered dose within four hours, infants managed in the same period of time to get rid of an average of only 57% of the test load. In addition, the infant was incapable of excreting urine of quite as low osmolar concentration as could the adult at the peak of diuresis. It should be added that other workers, whose results in general were in agreement with those of McCance and his group just quoted, differed in regard to the last point in that they succeeded in causing young infants, even premature infants weighing less than 2,500 g., to excrete urine fully as dilute as that produced by more mature subjects. Barnett and his colleagues (1952), for example, by imposing a water load of 40 ml. per kg. of body weight in premature infants reduced the urine concentration of their subjects to the level of 40 to 60 m.osmol./1. at the moment of maximal diuresis, which is the same as saying that they were unable to bring out evidence of renal functional immaturity even in their very small patients, so far as the ability to eliminate superfluous water was concerned. They made the point, however, that the ability to excrete urine of low osmolar concentration is a function of postnatal age, rather than of body weight. Thus, their patients aged 5 to 8 days showed a limited capacity to excrete dilute urine, while another subject, a premature infant 36 days of age whose body weight had reached only 2,460 g. at the time of the test, reacted to the water load in a manner comparable to that of an adult.

In this connexion the investigations of Ames (1953) should be mentioned. Although her primary goal was to explore the function of the posterior hypophysis in the first days after birth and to learn whether the newborn infant's kidney would respond to antidiuretic hormone, her studies brought out interesting aspects of the process of maturation. Water administration comparable to that used in the experiments referred to a moment ago disclosed that, in general, infants less than 3 days of age exhibit little, if any, diuresis in response to a water load. This situation changes rapidly, however, with increasing postnatal age and by one month after birth all infants in her study were capable of excreting 85% or more of the administered load within the course of two hours. One very small infant of birth weight 1,200 g. excreted only 50% of the administered water load within two hours at the age of 4 days, but by 12 days of age accounted for 100%. Since no water diuresis could be demonstrated in infants younger than 3 days of age, no response to injected antidiuretic hormone was expected or found ; but in older infants, that is, older than 3 days of age, who were showing a brisk diuresis in response to administered water, injection of as little as 0·5 milli-unit of pitressin intravenously invariably checked diuresis promptly. When infants less than 3 days of age were subjected to a period of thirsting of six or eight hours' duration and their urine collected and analysed for anti-diuretic hormone, relatively large amounts of the hormone were demonstrable, the average concentration being $1{\cdot}25 \pm 0{\cdot}25$ milli-units per ml. This proves that the posterior hypophysis is indeed capable of functioning at this age and of responding to the stimulus of mild thirst.

Liver function is difficult to measure at any age, and few investigators have been bold enough to attempt to observe maturation of any single component of this complicated field. Mollison and Cutbush (1949) took advantage of the accessibility of the umbilical vein in infants less than six hours old to inject bromsulphalein and measure the speed of its disappearance from circulation. In general, the rate of clearance was very much slower in these infants than it was in adults to whom an analogous

dose of 5 mg./kg. body weight had been given. The difference was ascribed to immaturity of hepatic excretory function. Their patients were followed long enough to observe the severity of physiological jaundice appearing in the course of the next few days, and no gross difference was found, in regard to bromsulphalein clearance, between those who later became jaundiced and those with lower degrees of bilirubinaemia. A somewhat similar study was carried out by Yudkin, Gellis and Lappen (1949) in which, again, bromsulphalein was administered intravenously to infants at various ages up to 9 days. Excretion was delayed in all. Although the degree of delay diminished with increasing age of the subjects, the rate of excretion was still sluggish in a 9-day-old veteran, the oldest one included, in comparison with adult standards. It would seem obviously desirable to pursue such studies long enough to learn when the mature level of bromsulphalein excretion is reached.

Excretion of bilirubin by young infants was studied by Fashena (1948) in relation to the occurrence of physiological jaundice of the newborn. Functional immaturity of the liver had long ago been postulated on theoretical considerations as one of the plausible determinants of neonatal jaundice, since no satisfactory correlation could be found between the degree of bilirubinaemia and the postnatal fall of haemoglobin concentration, red blood cell count or haematocrit level in the peripheral blood. Determination of the velocity of excretion of bilirubin (Weech, Vann and Grillo, 1941) as a liver function test has the double advantage that it employs in the load test a natural substance, rather than a totally extraneous one like bromsulphalein, and that it can be carried out without risk in the presence of hyperbilirubinaemia and clinical jaundice. All infants included in the study were tested during the first week of life. Those whose blood before loading showed a serum bilirubin level higher than 2·4 mg./100 ml. invariably displayed sluggish excretion of bilirubin, with a velocity constant lower than $2{\cdot}0\times10^{-3}$ mg. units. (The smaller the constant, the more limited is excretory function.) Those whose serum bilirubin level was lower than 1 mg./100 ml. before application of the test had a velocity constant equal to or greater than $2{\cdot}8\times10^{-3}$, reflecting satisfactory excretory function. In four infants who exhibited impaired excretion during the course of hyperbilirubinaemia and physiological jaundice, a second test repeated after the lapse of four to eight days showed that the velocity constant had now risen to normal level. The inference seems clear that many, not all, infants have immature hepatic excretory function for bilirubin during the first few days following birth, and that in the course of time mature function can be expected to develop spontaneously.

Many liver function tests which can be employed in older subjects in the study of disease have yielded little more than confusion when applied to young infants in an effort to measure the maturational process, so that useful information extends but little farther than the brief summary of work just cited. A new area has recently been opened up, however, which bids fair to add greatly to our knowledge of physiological development. I refer to the maturation of hepatic cellular enzyme systems. An early lead was given by the observation of Levine, Gordon and Marples (1941) that premature infants fed a high-protein diet without ascorbic acid excreted large amounts of hydroxyphenyl compounds in their urine, that mature infants would excrete these substances only if fed rather large amounts of the precursor amino-acids d, l-phenylalanine or l-tyrosine, and that in either premature or mature infants who showed the trait the excretion of these unusual hydroxyphenyl compounds could be promptly abolished by administration of large amounts of ascorbic acid. The phenomenon when it was first studied was recognized as having attributes of a maturational episode, but little attention was for a time attached to the possibility of its being localized in hepatic cells. Quite recently Kretchmer, Levine, McNamara and Barnett (1956) have devised techniques for studying soluble enzyme systems extracted from hepatic cells obtained from human livers, and have been able to measure the progressive development of specific enzyme constellations such as the tyrosine oxidizing system. Premature infants, full-term infants and adults formed three contrasting groups, with enzyme activity increasing in proportion to the figures 1 for prematures, 5 for mature infants and 20 for adults, whether comparison was made on the basis of wet weight of liver tissue originally used as source, milligrams of nitrogen in the enzyme solution, desoxyribonucleic acid content of the homogenate of liver cells or surface area of the subject. These initial studies explored only the tyrosine oxidizing system. In a subsequent extension of the work Kretchmer, Levine and McNamara (1957) demonstrated a relative lack of p-hydroxyphenylpyruvate oxidase activity in the livers of small infants, which could be partly overcome *in vitro* by the addition of relatively large quantities of ascorbic acid. The response of this particular enzyme system to ascorbic acid seemed to be dependent upon the weight of the infant, again suggesting a maturational phenomenon.

The fact that immaturity of these highly specific

hepatic cell enzyme systems results in urinary excretion of substances not ordinarily found there affords certain promise of an impending flood of new discoveries in the general picture of maturation of liver function. The element of chance ordinarily inherent in divination of the future is entirely removed from this particular prophecy by recent demonstration of the pattern of urinary amino-acid excretion in foetuses, premature infants, and mature infants of various ages. Norton, Pratt and Hasselmeyer (1954) have confined their study almost entirely to premature infants, while Woolf and Norman (1957) extended theirs to include a variety of ages and stages of maturity. The pattern is a complicated one but at the same time strongly consistent in the appearance and disappearance of individual components. This consistency applies not only to the excretion of amino-acids but to that of other substances as well—creatine, taurine, and various sugars, for example. Doubtless not all of them are controlled by enzyme systems residing exclusively in the liver, but it seems a reasonable prediction that most of them are and that closer study of liver function will eventually clarify the developmental picture. The fact that the waxing and waning pattern of urinary amino-acids represents a feature of developmental maturation is borne out by their spontaneous disappearance in the course of a few months.

The prothrombin level of the young infant's plasma follows a course which suggests a developmental evolution influenced in part by liver function, in part by the ingestion of prothrombin precursors in the food, and in considerable part also by the formation of precursors within the alimentary tract as a by-product of growth and metabolism of contaminating bacteria. The vagaries of the prothrombin story in early life depend a great deal on methods used in analysis, and complete agreement has not yet been reached among all authorities. Nevertheless, the general outlines are clear and I shall take the liberty of presenting them more or less in Quick, Murat, Hussey and Burgess's (1952) terms. When the mother has received no vitamin K during pregnancy beyond that contained in the diet, the prothrombin as measured by the one-stage method is found to be at about the same level at term in the mother's blood, the cord blood, and the infant's blood on the day of birth. On application of the two-stage method, which reveals not only active and available prothrombin but also reserves of prothrombinogen in inactive form, the mother's blood is found to have a considerable stock of prothrombinogen, a reserve which can easily be augmented still further by giving her additional vitamin K. In the newborn infant, however, administration of vitamin K on the day of birth has no immediate effect on his prothrombin level, just as administration to the mother before delivery has no influence on the active prothrombin content of the infant. He appears incapable of manufacturing prothrombinogen within the first two to four days after birth, and his active prothrombin concentration may even fall to a lower level, reaching a nadir generally on the third day of life. Thereafter it begins to rise and by the end of the first week or a little longer has once more reached the level which was present at birth. Reserves of prothrombinogen build up more gradually in the infant's blood, and as much as a year may elapse before the level has reached that which an adult usually shows. The pace of accumulation of reserves of inactive prothrombin may be retarded by liver trouble, by obstructive lesions of the upper alimentary tract which interfere with bacterial colonization of the lower tract and by persistent administration of antibiotics which likewise inhibit the growth of a normal intestinal flora.

Mention of infection, in this instance a beneficent one, leads naturally to discussion of developmental immunology, the acquisition of defence against harmful infections. The subject may be divided into three sections : mechanisms of defence transferred from mother to child ; mechanisms produced by the infant independently of contact with specific infecting agents ; and, finally, development of resistance orientated specifically toward a particular agent of disease with which the infant or child has come in contact in some form—dead (vaccine) or alive (infection).

A good deal of accurate quantitative information is available concerning transplacental conveyance of humoral immunity. It has long been known that diphtheria antitoxin concentrations in the blood of a mother and in the cord blood of her infant at term are essentially equal. The premature infant is not always quite so well off ; and if he is very young and immature, his mother's blood will usually show a considerable excess of antitoxin. Osborn, Dancis and Rosenberg (1952) set the crucial maturity point at a birth weight of roughly 2 kg., in that infants smaller than this limit were more apt than not to have an antitoxin titre lower than that of their mothers. After delivery, the infant receives no significant increment of diphtheria antitoxin from his mother, regardless of whether he nurses her colostrum; and from birth on, there begins a logarithmic descent of the antitoxin level which leaves him devoid of adequate protection from this source from the age of about 4 to 6 months onward, if no additional steps are taken.

Placental transfer of other specific defence agents has been similarly documented. A well known example is the postnatal curve of blood concentration of bactericidal antibodies against *Haemophilus influenzae*, plotted against age, which was long ago published by Fothergill and Wright (1933). The newborn infant has a significant antibody titre, which then falls rapidly so that by the age of 3 to 6 months specific antibody can no longer be measured. Not until the age of 3 years does the curve begin to rise again, and the authors brought out clearly in their publication the fact that the age incidence of *H. influenzae* meningitis reaches its peak during the period between 3 months and 3 years of age when specific antibody against this organism is most difficult to detect.

The age incidence of measles clearly suggests that immunity is passively transferred from the mother before the infant is born, and that the substance responsible for immunity gradually diminishes by attrition, becoming unreliable as an effective defence from about the age of 6 months onward. This interpretation was widely accepted on epidemiological evidence long before titration of measles antibody became technically feasible. Not all specific infections behave alike, however. Chickenpox and whooping cough frequently occur within a few weeks after birth, while mumps in infants less than 1 year of age is distinctly rare. We still lack accurate information regarding the defences against a number of infections, and in many instances we are quite uncertain how much resistance depends on humoral as opposed to non-humoral agencies.

In our search for information we must of necessity resort to certain indirect methods of investigation, less closely orientated toward specific infections. While it seems unlikely that the gamma globulin fraction of plasma is composed entirely of specific antibodies, a degree of parallelism undeniably exists between serum gamma globulin concentration and resistance to a variety of infections. Studies of the gamma globulin fraction of plasma in mother and foetus indicate that from an early stage of pregnancy, perhaps even as early as the beginning of the second trimester, the concentrations in the two bloods are virtually identical. At term the concentrations have been shown to be essentially the same in cord blood and in maternal blood (Orlandini, Sass-Kortsak and Ebbs, 1955). From this point on, the infant's plasma gamma globulin level commences a gradual fall which reflects the general rate of attrition of plasma protein components which are not being renewed by active production. Gitlin (1957) gave the half-life of a preparation of gamma globulin as 20 days when radioactivity was the basis of measurement, 45 days when immunochemical methods were used. It seems reasonable to expect that, because of known variations in the physical and chemical behaviour of individual plasma proteins, different rates of spontaneous attrition of individual specific antibodies will be found. In general, what has been learned in the laboratory concerning the disappearance of gamma globulin from an infant's blood in the early weeks of his independent existence following birth is entirely consistent with what is known of his gradual loss of resistance against certain infections.

Even the newborn infant possesses some humoral defence against infection which is independent of specific antibodies. The all-purpose defence on which most attention has recently been focused is the properdin system, initially described by Pillemer, Blum, Lepow, Ross, Todd and Wardlaw (1954). According to Hinz (1956) properdin, itself a protein of high molecular weight, is demonstrable in plasma in approximately equal concentration at all ages. The properdin system, to be effective in controlling infection, must include interaction of properdin, complement and Mg^{++} ion. Although the exact role of the properdin system in early life has not yet been fully assessed, some explanation is required for the asymptomatic course which most infants succeed in following between the time when the antibodies they have received from their mother give out and the time when their own antibody production has reached an adequate level. It would seem highly probable that mechanisms of defence are operating on the young infant's behalf, of which we have as yet only imperfect knowledge, such as the circumstances which govern phagocytosis, or about which we know nothing at all. We lack a satisfactory explanation of the paradox that young infants from an early age commonly harbour virulent strains of staphylococci in the nasopharynx, and yet the frequency of significant staphylococcal infections remains on the whole surprisingly low.

Chemical analyses of plasma for its total content of gamma globulin, whether the analytic method is that of electrophoresis or the cruder but nevertheless serviceable titration of zinc turbidity (Harris, 1952; Orlandini *et al.*, 1955), show that the concentration reaches its low point at the age of about 3 months, after which it starts a gradual rise. The slope of the ascending curve of gamma globulin concentration has not been shown to be clearly dependent on the number of recognized infections experienced by the individual subject. Raffel (1953) cites anatomical evidence that bone marrow of infants does not contain plasma cells until the age

of 3 months. This finding is consistent with the commonly accepted belief that the plasma cell is the site of production of specific antibodies, and with the timing of the point on the age axis at which plasma gamma globulin begins to be renewed from autochthonous sources. It leaves unexplained, however, the demonstrated ability of an infant much younger than 3 months of age to respond to contact with an appropriate antigen by production of antibody in significant quantities, as will be described later.

Studies of specific antibody formation in response to spontaneously acquired infections, whether clinical or subclinical, are surprisingly few. Fothergill and Wright's (1933) measurements of the curve of antibody titre against *H. influenzae* in relation to age have already been mentioned, with their rise in titre beginning at age 3 years. To judge from the information gathered on this subject regarding antibodies to the three chief types of poliomyelitis virus, before the widespread use of vaccine, the likelihood that any given individual would show significant levels of one, two, or all three antibodies depended on a host of variables—his age, the number of people in the family, rural or urban setting, school contacts, housing standards and standards of general hygiene, as well as exposure to epidemic infection (Melnick, Paul and Walton, 1955; Sabin, 1955). Important background information of this kind in relation to poliomyelitis will obviously become entirely unattainable as soon as prophylactic administration of vaccine becomes universal. The chances of obtaining comparable information concerning humoral antibodies to various bacterial infections seem likewise to be evaporating in the face of the widespread application of interfering factors in the form of effective antibacterial agents.

A vast field remains open for future study, of course, in the measurement of the infant's or child's response to vaccines and other agents given for prophylactic purposes. Results published thus far would seem to indicate that when a three-pronged agent like the popular combination of tetanus and diphtheria toxoids and pertussis bacterial vaccine is injected into young infants, beginning at 1 week of age, an apparently different response is obtained to each of the three components (di Sant'Agnese, 1949). Successful production of antibodies against tetanus toxin indicates that even at this early age active immunization is feasible. On the other hand, the less impressive development of measurable antibodies to diphtheria toxin and to pertussis leaves unanswered whether the fault lies with the infant, in an immature mechanism for responding to a particular agent, or in the nature of the antigen used, or possibly in the interfering effect of residual specific antibody originally transmitted *in utero*. At a later age, antibody production in response to the same agent is much more active.

Certain infections evoke different responses at different ages, usually producing more serious disease the younger the subject. A number of examples come to mind. Congenital toxoplasmosis, transmitted from mother to infant *in utero*, is almost invariably more serious than the disease acquired in later life. This difference may be one of dosage, but thus far proof is lacking. Congenital syphilis in the pre-penicillin era was far more lethal to the foetus and infant than to the mother. Among severe infections caused by *H. influenzae*, purulent meningitis is most frequent between the ages of 2 months and 2 years, almost 80% of all examples of influenzal meningitis falling in this sharply limited age zone. Acute epiglottitis or infection of the supraglottic structures caused by the same organism is even more frequently associated with bacteraemia, can also be fatal all too frequently, and yet is hardly ever encountered in a patient younger than 2 years of age. Infection with Coxsackie B virus, according to Gard (1954) and Johnsson (1954), has produced three distinct syndromes, depending on the age of the patient: a fatal myocarditis in very young infants, a form of 'aseptic meningitis' which leaves no permanent residua in older infants and children, and in adults pleurodynia or so-called epidemic myalgia. The Sendai virus, first isolated by Kuroya, Ishida and Shiratori (1953) in Japan in 1951, was originally recovered from the lungs in fatal cases of pneumonitis which occurred in newborn infants. Later, an apparently identical virus was grown from the respiratory tract of adults suffering from a non-fatal form of an influenza-like syndrome, and Matsuzawa and his colleagues (1953) still later isolated the same virus from a child who recovered after a 40-day illness with respiratory symptoms. In the last instance a rise in antibody titre was demonstrated for the first time in the convalescent patient. Jensen, Minuse and Ackermann (1955), to whom a sample of the virus was sent soon after its initial isolation, found significant levels of antibody in a large number of sera collected from various parts of the State of Michigan. Some of these American sera were fresh, others had been preserved for as long as 19 years, and in no instance was historical evidence obtainable of a corresponding clinical infection. One is left to speculate whether the diverse patterns of clinical disease produced at different ages by what are believed to be identical infecting agents depend upon insidiously acquired specific immunity, which must of necessity have been

inadequate to achieve full protection, or whether they reflect different levels of immunological maturation.

In bringing this fragmentary and tentative consideration of growth and development to a close, it is conceivably more prudent as well as more informative to take note of known omissions than to attempt to survey the ground covered. Nothing has been said of intellectual growth, of emotional maturation, or social adaptation. Important as these are, all of them, in the assessment of a clinical situation, they represent areas of concern in which the physician's responsibility is subordinate to that of the family unit, the school, the community. The broad field of symptomatic expression with relation to age of patient has been almost completely ignored, and that companion territory—the age incidence of specific diseases and syndromes, which goes so far to justify paediatrics as a specialty within the broad boundaries of general practice—has received but scant mention. Only a beginning has been made in indicating lines of investigation which seem to hold promise for the near future. There is no need to dwell on the diminutive scope of what we now know in comparison with what is yet to be learned. Growth and development, with their vagaries and their ever-changing manifestations, keep a physician on the alert and add flavour of their own to the pursuit of the Hippocratic tradition among those patients who have not ceased to be children.

I would express my deep obligation to my paediatric colleagues on the staff of Babies Hospital in New York for the help and inspiration they have given over the past several months in the shaping of these thoughts. The task of setting them down in organized form has been a happy one, constantly lightened by awareness of their intent, to pay tribute to the memory of the man whom these lectures honour, Sir Leonard Parsons.

References

Ames, R. G. (1953). *Pediatrics*, **12**, 272.
Apgar, V., Girdany, B. R., McIntosh, R. and Taylor, H. C. (1955). *Ibid.*, **15**, 653.
Ashton, N., Ward, B. and Serpell, G. (1954). *Brit. J. Ophthal.*, **38**, 397.
Barnett, H. L., Vesterdal, J., McNamara, H. and Lauson, H. D. (1952). *J. clin. Invest.*, **31**, 1069.
Cook, C. D., Brodie, H. R. and Allen, D. W. (1957). *A.M.A. J. Dis. Child.*, **93**, 9.
Crosse, V. M. and Evans, P. J. (1952). *A.M.A. Arch. Ophthal.*, **48**, 83.
Day, R. and Du Pan, R. M. (1949). *Amer. J. Dis. Child.*, 77, 109.
——, Curtis, J. and Kelly, M. (1943). *Ibid.*, **65**, 376.
di Sant'Agnese, P. A. (1949). *Pediatrics*, **3**, 20.
Fashena, G. L. (1948). *Amer. J. Dis. Child.*, **76**, 196.
Fothergill, L. D. and Wright, J. (1933). *J. Immunol.*, **24**, 273.
Gard, S. (1954). *Acta paediat. (Uppsala)*, **43**, *suppl.* 100, p. 54.
Gitlin, D. (1957). *Pediatrics*, **19**, 657.
Harris, R. C. (1952). *Bull. N.Y. Acad. Med.*, **28**, 721.
Hinz, C. F., Jr. (1956). *Ann. N.Y. Acad. Sci.*, **66**, 268.
Jensen, K. E., Minuse, E. and Ackermann, W. W. (1955). *J. Immunol.*, **75**, 71.
Johnsson, T. (1954). *Arch. ges. Virusforsch*, **5**, 384.
Jonxis, J. H. P. (1949). In *Haemoglobin* [Barcroft Memorial Conference], p. 261, F. J. W. Roughton and K. C. Kendrew, editors. London.
Kretchmer, N., Levine, S. Z. and McNamara, H. (1957). *A.M.A. J. Dis. Child.*, **93**, 19.
——, ——, —— and Barnett, H. L. (1956). *J. clin. Invest.*, **35**, 236.
Kuroya, M., Ishida, N. and Shiratori, T. (1953). *Tohoku J. exp. Med.*, **58**, 62.
Levine, S. Z., Gordon, H. H. and Marples, E. (1941). *J. clin. Invest.*, **20**, 209.
Matsuzawa, M., *et al.* (1953). *Virus (Osaka)*, **3**, 336.
McCance, R. A. (1950). *Amer. J. Med.*, **9**, 229.
—— and Widdowson, E. M. (1953). *Proc. roy. Soc. B*, **147**, 488.
——, —— (1954). *Archives of Disease in Childhood*, **29**, 488.
——, Naylor, N. J. B. and Widdowson, E. B. (1954). *Archives of Disease in Childhood*, **29**, 104.
Melnick, J. L., Paul, J. R. and Walton, M. (1955). *Amer. J. Publ. Hlth*, **45**, 429.
Mollison, P. L. and Cutbush, M. (1949). *Archives of Disease in Childhood*, **24**, 7.
Norton, P. M., Pratt, E. L. and Hasselmeyer, E. (1954). *A.M.A. J. Dis. Child.*, **88**, 659.
Orlandini, T., Sass-Kortsak, A. and Ebbs, J. H. (1955). *Pediatrics*, **16**, 575.
Osborn, J. J., Dancis, J. and Rosenberg, B. V. (1952). *Ibid.*, **10**, 450.
Pillemer, L., Blum, L., Lepow, I. H., Ross, O. A., Todd, E. W. and Wardlaw, A. C. (1954). *Science*, **120**, 279.
Quick, A. J., Murat, L. G., Hussey, C. V. and Burgess, G. F. (1952). *Surg. Gynec. Obstet.*, **95**, 671.
Raffel, S. (1953). *Immunity, Hypersensitivity, Serology*, p. 72. New York.
Rubin, M. I., Bruck, E. and Rapoport, M. (1949). *J. clin. Invest.*, **28**, 1144.
Sabin, A. B. (1955). *Wld Hlth Org.*: Monogr. Ser. No. 26, p. 297. Geneva.
Stevenson, S. S. (1943). *J. clin. Invest.*, **22**, 403.
Vesterdal, J. and Tudvad, F. (1949). *Acta paediat. (Uppsala)*, **37**, 429.
Villee, C. C. A. (1957). *Josiah Macy, Jr., Foundation Conference on Prematurity*, Princeton.
Weech, A. A., Vann, D. and Grillo, R. A. (1941). *J. clin. Invest.*, **20**, 323.
Wilson, J. L., Reardon, H. S. and Murayama, M. (1948). *Pediatrics*, **1**, 581.
Wolf, A. and Cowen, D. (1954). In *Neurology and Psychiatry in Childhood*, R. McIntosh and C. C. Hare, editors. *Res. Publ. Ass. nerv. ment. Dis.*, vol. 34, p. 199, Baltimore.
Woolf, L. I. and Norman, A. P. (1957). *J. Pediat.*, **50**, 271.
Yudkin, S., Gellis, S. S. and Lappen, F. (1949). *Archives of Disease in Childhood*, **24**, 12.

INTERSTITIAL MONONUCLEAR PNEUMONIA

A Cause of Sudden Death in Gurkha Infants in the Far East

BY

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For the past few years interstitial mononuclear pneumonia has been recognized as a cause of sudden death in infancy in America and elsewhere (Gruenwald and Jacobi, 1951). The following report is a result of an investigation prompted by the occurrence over some years of cases of sudden or rapid death in Gurkha infants in Malaya and Hong Kong for which a completely satisfactory explanation was lacking. Many had been classified as bronchopneumonia although the pathological findings were not typical. On religious grounds permission for post-mortem examination was often refused and diagnosis was made on clinical grounds which again were often atypical. Accurate clinical descriptions were scanty when death occurred in isolated stations, and indeed at the beginning of the investigation it was by no means certain that a primary respiratory infection was the cause.

Material

The 18 cases described here were all proved histologically at necropsy. They were derived from the re-investigation of past fatal cases of which notes and pathological material were available (Cases 1—7), and from a series of 58 patients with fulminating respiratory infections of whom 32 died; permission for post-mortem examination was obtained in 19 cases (Cases 8—18).

Clinical Description

The clinical histories are summarized in Appendix I. The ages of the babies varied from 1 to 7 months, averaging 3 months. Ten of the 18 cases were aged 2 months or under. There was no seasonal incidence and the cases were for the most part sporadic over a wide area with the exception of one period when two cases were admitted to one hospital in one month and a further two cases within the next three months (Cases 1—4). The previous health of both the mothers and the children was, to outward appearances, usually excellent.

Immediately preceding illness of a mild character for one or two days occurred in nine cases before the acute respiratory symptoms appeared or the baby was found dead in bed. These were most often mild diarrhoea or mild 'feeding problems'. Two cases gave a history of respiratory illness.

Three babies were found dead in bed and a fourth died on being picked up. The rapidity of the process was the outstanding feature in all the other cases. This varied from under one hour to a maximum of 36 hours. The change to an obviously very serious condition was always extremely rapid and at times could be described as sudden. Collapse was a prominent feature and there was respiratory distress and cyanosis. Respiration was laboured or grunting but the rate was only moderately increased. It sometimes became Cheyne-Stokes in character before death. Physical signs in the chest other than the use of ancillary muscles and indrawing of the ribs were very uncommon. The temperature was nearly always either normal or subnormal with a cold skin and flaccid limbs.

The differential diagnosis from the acute bacterial infections was not always clear cut. Pathologically proved cases of bacterial infections on occasion presented almost as dramatically as these described and with a similar absence of chest signs. However, no such cases were ever found dead in bed. Further, interstitial mononuclear pneumonia could occasionally present in a manner quite similar to a fulminating bacterial pneumonia as for example in Cases 10 and 13.

It is thought that the condition may not always be fatal provided adequate treatment is immediately available. That this may be so is suggested by a few very similar cases which survived, examples of which are given in Appendix II.

Pathology

Externally the bodies of these children showed little or nothing abnormal. In a few instances frothy fluid was to be seen coming from the nose and possibly some cyanosis might exist, but usually there was nothing to point to a respiratory mode of death.

Internally a few petechial haemorrhages had occurred on the surfaces of the thoracic viscera and the lungs showed a slight emphysema with frequent congestion towards the bases. The lungs were usually well aerated but a patchy, dark-coloured appearance suggestive of atelectasis occurred in the area which later, on microscopical examination, proved to be affected by the pneumonic process. It was only with difficulty that any fluid could be expressed from the respiratory passages.

Microscopically, there were four principal features which were constantly present in a greater or less degree in all cases, namely, (1) emphysema, (2) thickening of the alveolar walls, (3) mononuclear cell infiltration, (4) alveolar exudate.

Perhaps the most striking feature on first examination was the emphysema, which affected all areas not directly involved in the pneumonic process. Here the alveoli were grossly distended and often ruptured. This change was most noticeable by contrast with the greatly thickened alveolar walls of the affected areas which were adjacent to them.

Thickening of the alveolar walls was perhaps the most characteristic feature of the lesion. The walls were swollen and often heavily infiltrated by large mononuclear cells and lymphocytes. There was also some congestion with red cells. The thickening was sometimes so extreme as entirely to obliterate the alveoli or these might have been dilated with fluid exudate. Adjacent areas of extreme alveolar thickening produced a solid appearance of that part of the lung. There was, however, no particular relationship to any anatomical structure such as the bronchi, where these changes were most marked. Although the inflamed tissue was scattered widely throughout the lung, it was usual for not more than half the total lung tissue to be completely involved. Exudate and emphysema, however, were spread more widely.

The exudate consisted of pale, eosinophilic staining fluid which contained islands of mononuclear cells. These were characterized by a clear homogeneous cytoplasm devoid of granules and a monocyte type of nucleus which occasionally showed a dense chromatin network and a coarse reticular pattern. These cells were of considerable size, being up to about 15 or 20μ in diameter, and were almost round or oval. A few smaller cells were also found in the exudate. These closely resembled lymphocytes. In none of these cells could virus or other inclusion bodies be demonstrated, although careful search was made after appropriate staining by Dominich's method, phloxine-tartrazene and Giemsa's stains. There was also no sign of any bodies which might be interpreted as being yeasts or *Plasmodia*.

A similar cellular morphology was seen in the cells infiltrating the alveolar walls but here the addition of a few red cells was not unusual.

In two cases there were also numbers of polymorphs, particularly within and around the smaller bronchi. It is to be presumed that these cases had become involved in a secondary bronchopneumonia.

The heart generally showed both epicardial and endocardial petechiae and right-sided dilatation. The myocardium was, however, histologically normal. Petechial haemorrhages were also present on the surface of the pleurae. The brain showed congestion and some oedema and both liver and spleen were invariably congested. The other organs showed nothing unusual.

Discussion

The cases described here are very similar both clinically and pathologically to those reported by Gruenwald and Jacobi (1951) from Brooklyn when investigating sudden death or rapidly fatal illness in infants. Davison (1945), analysing the causes of infant deaths in Birmingham, has pointed out that only a small percentage of deaths allegedly due to suffocation were due to that cause but that the majority were due to acute fulminating infection. Nevius (1953) also stressed the same point. Werne and Garrow (1947) and Carroll (1954) confirmed the work of Gruenwald and Jacobi that interstitial pneumonia was a common cause of sudden unexpected and apparently unexplained death in infants. The former stress that aspiration of vomit is not an uncommon finding in subjects dying of other causes. They consider that it should, with rare exceptions, be regarded as an agonal phenomenon. This is also confirmed by Tudor (1955). Although clinically the distinction is not always clear cut, the cases in this series like those of Gruenwald and Jacobi differ from the hyperacute bacterial pneumonias in the extreme suddenness of their onset, the prominence of collapse with low or normal temperature, and the frequent absence of auscultatory signs in the chest. There is indeed sometimes doubt in the doctor's mind if the condition is primarily respiratory in origin. They differ clinically and pathologically from the descriptions of interstitial plasma-cell pneumonia reported by Baar

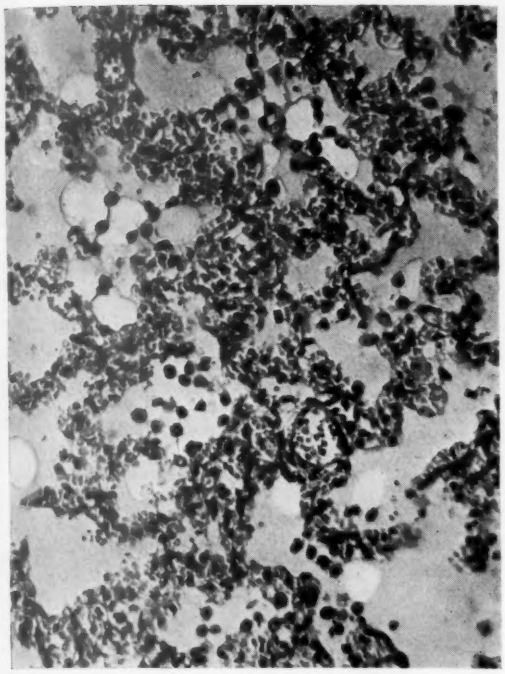

FIG. 1.—Cellular exudate within the alveoli. (× 195.)

(1955), Deamer and Zollinger (1953) from Switzerland, Vaněk, Jírovec and Lukeš (1953) in Czechoslovakia, Ahvenainen and Hjelt (1954) in Finland, and Lunseth, Kirmse, Prezyna and Gerth (1955), Adams (1941, 1948) and Sternberg and Rosenthal (1955) in America. These were all much more prolonged illnesses often of several weeks' duration.

Since the condition was occurring in an Asian community, the role of thiamine deficiency was considered, either as causal or aggravating. Clinically the condition was dissimilar from the accepted descriptions of infantile beri beri by Hoobler (1928), Strong (1945) and Nelson (1950). In these the onset was over some days of cardiac failure with oedema. There were attacks of colic and also of rigidity suggesting central nervous involvement. Fehily (1941) describes the acute stage of infantile beri beri as similar to a cardiac attack or bronchopneumonia with normal or subnormal temperature but with certain typical prodromata which were absent here. Such cases represented only a small proportion of the total in a community where infantile beri beri was rife. These conditions did not obtain in this series although a moderate thiamine deficiency in the breast milk is common in Gurkha mothers. Eight controls gave thiamine figures from 5·1 to 18 μg. %, averaging 9·2 μg. %. This is low in comparison with the accepted normal in the United Kingdom of 14 to 18 μg. % (Kon and Mawson, 1950). In nine rapidly fatal cases of acute respiratory disease in Gurkha infants the level averaged 5·1 μg. % (nil to 19·4) and in 10 non-fatal cases 6·7 μg. % (nil to 20·4). It was also very low in three fatal cases of interstitial pneumonia and it is therefore possible that thiamine deficiency may have played an aggravating role in the present series of cases.

It will be noted that out of 19 consecutive necropsies 11 cases showed the histological changes of interstitial mononuclear pneumonia. Eight showed the features of a bacterial pneumonia. This is not to be interpreted as the relative incidence of the two types of disease in fulminating cases. As cases had died during or as the result of long journeys to hospital, regimental medical officers were encouraged to retain such patients in the small regimental hospitals which were equipped with an enlarged pattern of the 'Queen Charlotte' oxygen box, ice cooled, and the necessary antibiotics. This undoubtedly saved the lives of many cases of fulminating bacterial infections but only a few proved cases of interstitial pneumonia were thus treated.

This arrangement also precluded effective bacterial and viral investigation.

Summary

The clinical and pathological findings in 18 cases of interstitial mononuclear pneumonia in Gurkha

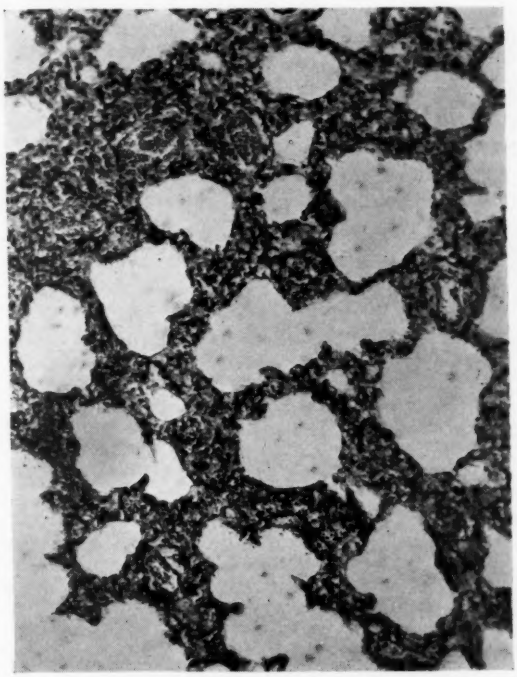

FIG. 2.—Thickening of alveolar walls and emphysema. (× 99.)

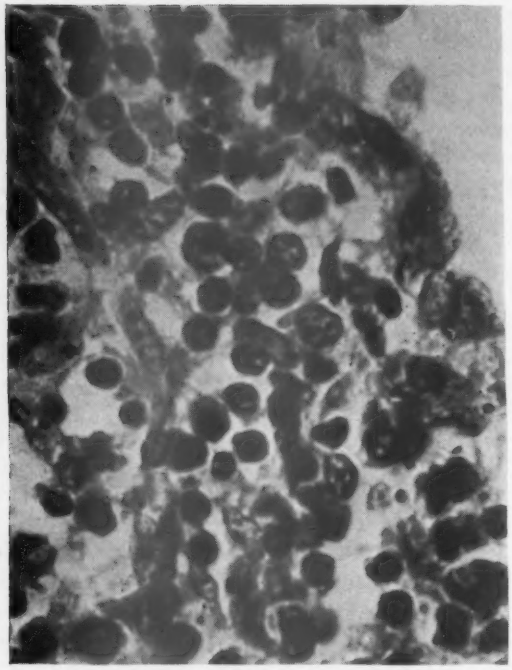

FIG. 3.—Thickened alveolar wall showing cellular infiltrate. (×864.)

infants are described. Three non-fatal cases which were possibly of similar pathology are also described.

The condition is compared with certain other causes of rapid or sudden death in infants.

The aetiology is unknown. No histological evidence of viral infection was found but laboratory investigation was of necessity very incomplete. Thiamine lack was considered as a cause but on the whole evidence was against it being other than a possible aggravating factor. There was no evidence of case to case infection.

The condition is apparently a highly fatal one but there is some suggestion that prompt oxygen therapy allied with antibiotics and thiamine may be successful.

Thanks are due to Lieutenant-Colonel D. Bell, R.A.M.C., for collecting much pathological material in the early stage of this investigation and also to Dr. I. A. Simpson and Miss E. B. Cheek, of the Institute for Medical Research, Kuala Lumpur, for the estimation of milk thiamine levels.

Many regimental and hospital medical officers took an active part, and much essential administrative help was given by Colonel P. J. Richards, D.S.O., O.B.E., and Colonel J. C. Reed, C.B.E., successive Assistant Directors of Medical Services, and Lieutenant-Colonel C. W. Maisey, O.B.E., Assistant Director of Army Health at Headquarters Malaya Command.

REFERENCES

Adams, J. M. (1941). *J. Amer. med. Ass.*, **116**, 925.
—— (1948). *Ibid.*, 138, 1142.
Ahvenainen, E. K. and Hjelt, L. (1954). *Ann. Med. intern. Fenn.*, **43**, 1.
Baar, H. S. (1955). *J. clin. Path.*, **8**, 19.
Carroll, G. J. (1954). *J. Pediat.*, **45**, 401.
Davison, W. H. (1945). *Brit. med. J.*, **2**, 251.
Deamer, W. C. and Zollinger, H. U. (1953). *Pediatrics*, 12, 11.
Fehily, Lydia (1941). *J. trop. Med. Hyg.*, **44**, 21.
Gruenwald, P. and Jacobi, M. (1951). *J. Pediat.*, **39**, 650.
Hoobler, B. R. (1928). *J. Amer. med. Ass.*, **91**, 307.
Kon, S. K. and Mawson, E. H. (1950). 'Human Milk.' *Spec. Rep. Rep. Ser. med., Soc., Res. Coun. (Lond.)*, No. 269.
Lunseth, J. H., Kirmse, T. W., Prezyna, A. P. and Gerth, R. E. (1955). *J. Pediat.*, **46**, 137.
Nelson, W. E. (1950). Mitchell-Nelson, *Textbook of Pediatrics*, 5th ed. Philadelphia and London.
Nevius, W. B. (1953). *J. med. Soc., N.J.*, **50**, 242.
Sternberg, S. D. and Rosenthal, J. H. (1955). *J. Pediat.*, 46, 380.
Strong, R. P. (1945). *Stitts Diagnosis, Prevention and Treatment of Tropical Diseases*, 7th ed., p. 1047. London.
Tudor, R. B. (1955). *Minn. Med.*, **38**, 41.
Vaněk, J., Jírovec, O. and Lukeš, J. (1953). *Ann. paediat. (Basel)*, **180**, 1.
Werne, J. and Garrow, I. (1947). *Amer. J. publ. Hlth*, 37, 675.
——, —— (1953). *Amer. J. Path.*, **29**, 633, 817.

APPENDIX I

Case 1. A girl aged 6 months with previous good health. Diarrhoea and vomiting had occurred for one day, two days before she was found dead in bed.

Case 2. A boy aged 2 months who had had bronchopneumonia when aged 1 month. He had been discharged from hospital two weeks before the terminal illness. While out of hospital he had had two attacks of respiratory distress with pyrexia which had cleared rapidly. On the morning of death he had vomited twice and had had several bouts of coughing. He was not seen by a doctor until after death.

Case 3. A boy aged 6 months, whose previous health had been normal. He had a slight cough and pharyngitis in the morning and that evening developed respiratory distress, the respiration at times becoming Cheyne-Stokes in character. His pulse was weak and irregular. There were no signs in the chest. He was placed in an oxygen tent and given penicillin, but died in the early morning.

Case 4. A boy aged 2 months whose previous health was good. He had been treated for diarrhoea for two days and had recovered. On the day he was to be discharged, there was sudden onset of respiratory distress with marked stridor and cyanosis. The temperature was 98·4° F. with no signs in the chest. He was treated with oxygen and coramine, but died three hours later.

Case 5. A girl aged 6 weeks whose previous health was good. She had had mild diarrhoea for a few days which had cleared, then some vomiting, and she was admitted to hospital as a feeding problem. Her temperature was 100° F. and she appeared slightly toxic. Nothing abnormal was found on examination. She was found dead in bed 10 hours after admission. No treatment had been given.

Case 6. A boy aged 1 month. He had a sudden onset of dyspnoea and crying. He was found to be cold with a pulse rate of 70 and respirations 35. There were no other abnormal physical signs. He was treated with oxygen, penicillin and coramine, but died 12 hours after admission to hospital.

Case 7. A girl aged 7 months with previous good health. There was no prodromal illness. She had a rapid onset of laboured grunting respirations and cyanosis. She vomited four times. Temperature 98·0° F., pulse 120, respirations 30. There were no abnormal physical signs other than the use of the ancillary muscles of respiration and some indrawing of the ribs. She was treated with aureomycin, penicillin and oxygen. She suddenly collapsed and died 12 hours after admission.

Case 8. A girl aged 2 months. Previous health was fair. There had been mild diarrhoea and vomiting for two weeks, but no great anxiety was felt. She was considerably better that day and evening, but she was found that night to be crying, gasping and cyanosed. Her limbs were hypotonic and there was some indrawing of the lower ribs. No other abnormal physical signs were found. She died at once before therapy could be given.

Case 9. A girl aged 7 weeks with previous good health. There was no prodromal illness. She was found in the morning to have a rapid, grunting respiration but was not markedly cyanosed. Temperature 99·2° F., pulse 130, respirations 44. There were no abnormal signs in the chest. The limbs were hypotonic. She was treated with oxygen, penicillin and chloramphenicol. She died the following morning.

Case 10. A boy aged 2 months. He was found in the morning to be pyrexial (temperature 102° F.), to be breathing rapidly and generalized rales were present in the chest. He was admitted to hospital 24 hours later and treated with oxygen, penicillin and cortisone. He died in six hours.

Case 11. A boy aged 6 weeks who had previous fair health. He had been considered to be a mild feeding problem for the previous two weeks and mother and child were admitted to hospital for instruction. The mother was wakened by a cry and found the baby unconscious, cold and cyanosed with grunting respirations. Pulse 50, respirations 44. There were no abnormal findings in the chest. The abdomen was distended. He was treated with oxygen, intravenous aureomycin, penicillin and nikethamide. No thiamine was given. He died one and a half hours later. Breast milk thiamine was 1·9 μg. %.

Case 12. A girl aged 2 months with previous good health. She had no prodromal illness and no choking incident was observed. She was found dead in bed.

Case 13. A boy aged 6 months with previous normal health. He had no prodromal illness. He was slightly off colour in the afternoon and rapidly deteriorated that evening. He was admitted to hospital in semi-coma. Temperature 102° F., pulse 140, respirations 36. There was no stridor and little cyanosis. There were generalized rales in the chest. He was treated with thiamine (50 mg. intramuscularly), penicillin, aureomycin and oxygen. His condition deteriorated further and he died 36 hours after the onset of the illness.

Case 14. A girl aged 3 months. Previous health fair. She had no prodromal illness. For two days, three weeks before the final illness, she had attacks of apnoea. During the night, before the fatal attack, she had three episodes of apnoea with rigidity and cyanosis.

On examination she appeared to have difficulty in breathing except when the head was extended. There was slight stridor when the head was flexed. Temperature 97·0° F., pulse 120, respirations 46. No other abnormal physical signs were present. No treatment was given, and 24 hours after admission to hospital the child suddenly became cyanosed, developed Cheyne-Stokes respiration and died. The mother's milk thiamine level was 4·2 μg. %.

Case 15. A boy aged 1 month with previous normal health. He had six loose stools the day before onset of the illness. He then suddenly collapsed, became unconscious, cold and cyanosed, with shallow, sighing, slow respiration. There were no abnormal signs in the chest. Temperature 96·0° F., pulse 120, respirations 18. He was treated in an oxygen tent and was given streptomycin. He showed some clinical improvement, but died on the way to hospital.

Case 16. A boy aged 6 weeks. His previous health was normal. For 24 hours he had been 'unwell' and had vomited once. The bowels were open normally. There was then a rapid onset of collapse. He was cold (temperature 97·4° F.) and the respirations were rapid. There were no abnormal signs in the chest but the abdomen was very distended and hard. He was considered to be a possible case of intestinal obstruction. No treatment was given and he died 50 minutes after admission to hospital.

Case 17. A boy aged 4 months, with previous normal health. He had no prodromal illness. His mother had mild diarrhoea and vomiting and the baby was admitted to hospital with her. He was found dead in his cot.

Case 18. A boy aged 2 months with previous normal health. He was brought to the doctor because he was whimpering and crying. Nothing abnormal was found then. On the following day he was picked up by his father because he was crying, and died immediately.

APPENDIX II

Case A. A boy aged 3 months. Both mother and child were healthy. He suddenly collapsed following a breast feed, but there was no choking incident. When seen two hours later in hospital the child was conscious, but cyanosed with hypotonic limbs and a cold skin. Temperature 98·0° F. (rectal), pulse 150, respirations 54. The respirations were grunting, the ribs indrawn and the accessory muscles were being used. There were no other

abnormal physical signs. He was treated with oxygen, penicillin, chloramphenicol, elixir of phenergan and intramuscular thiamine. There was a good response in two hours which was maintained until discharge from hospital five days later. The mother's breast milk thiamine level on the day of admission was 6·9 mg. %. After five days of 30 mg. daily, the milk thiamine level was 22·6 μg. %.

Case B. A girl aged 7 weeks. She had been in hospital for five days with gastro-enteritis, which had reacted well to sulpha therapy. On the morning she was awaiting discharge, there was a sudden onset of respiratory distress. The ribs were indrawn and the accessory muscles were being used, but there were no other abnormal signs in the chest. There was no cough. She was conscious and hydration was good, but there was slight neck rigidity and hypotonic limbs. The abdomen was distended. Temperature 99·6° F., pulse 150. She was treated in an oxygen tent and with penicillin, chloromycetin and intramuscular thiamine. By evening the respiratory rate had risen to 60, but the character was normal except that the alae nasi were working. Therapy was continued for six days and improvement was maintained. She was discharged well. The milk thiamine level was 8·4 μg. %.

Case C. A boy aged 4 months. He had a cough for one day and then an extremely rapid onset of respiratory distress. Temperature 101° F., pulse 180, respirations 30. He was conscious, well hydrated with normal skin temperature and normal muscle tone. However, he was cyanosed, the alae nasi were working and he was using the accessory muscles of respiration. There were no abnormal physical signs in the chest. He was treated in an oxygen tent with penicillin, chloramphenicol and intramuscular thiamine. He recovered rapidly and uneventfully. The milk thiamine level was 20·4 μg. %.

ADRENOCORTICAL HYPERPLASIA IN CHILDHOOD

BY

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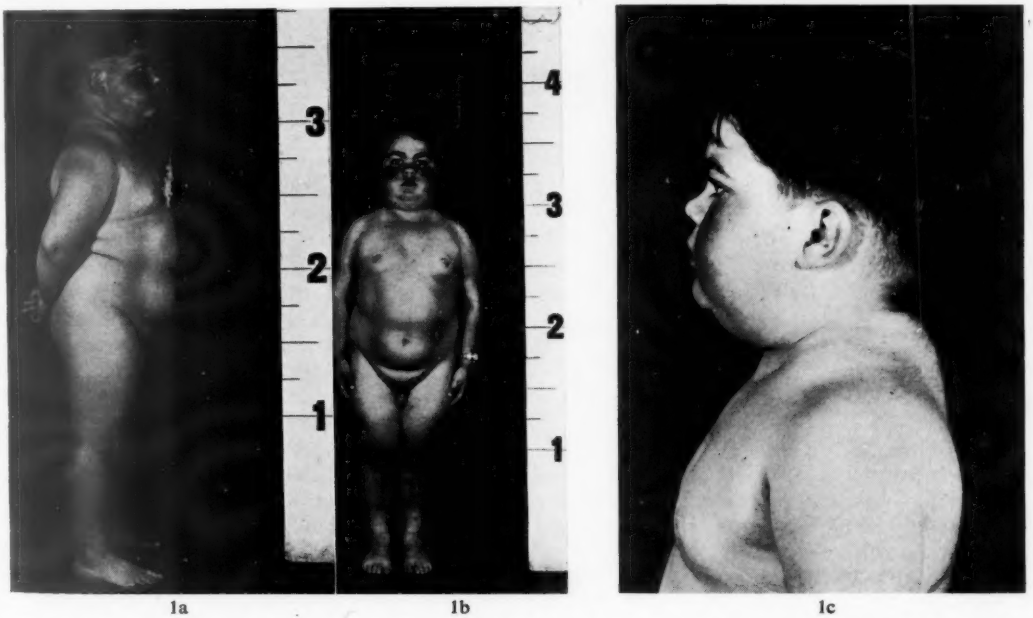
Adrenocortical hyperplasia is uncommon in childhood. It occurs as the adrenogenital syndrome (congenital virilism in girls) which has now been shown to be due to a congenital defect in the synthesis of cortisol by the adrenal cortex. In the United States its incidence is once in every 58,000 live births (Grumbach, 1956) and it has a recessive mode of inheritance. The disease is more easily diagnosed in females than in males and this is probably the reason for the higher observed incidence in girl babies.

Cushing's syndrome is a still more uncommon result of adrenocortical hyperplasia in children. Before 1949 this had not been described in a child under the age of 10 years (Wilkins, 1950) but in 1949 Chute, Robinson and Donohue described it in an 8-year-old girl. Twenty-two other cases of Cushing's syndrome under the age of 10 years have been reported and all were due to a tumour. One of the cases now to be described is a boy with Cushing's syndrome which had its onset at the age of 6 years; the other is a girl aged 2½ years with congenital virilism. Both cases illustrate some problems in the pathogenesis, diagnosis and treatment of adrenocortical hyperplasia in childhood.

Case Reports

Case 1. Robert, aged 8½ years, was admitted to the Derbyshire Hospital for Sick Children on February 6, 1956, with a history of failure to grow and increasing obesity for two years. There was nothing of relevance either in his family or in his past history.

On examination (Figs. 1a, b, c) his weight was 65 lb. (average for age 55·3 lb.). His height was 43·5 in. average for age 50·2 in.). His personality was very happy and his intelligence high. His cheeks were rosy. The obesity was of a 'buffalo-type' and there was a fine growth of black hair on his back and shoulders. Hair was growing out of his nostrils. There was no axillary



1a 1b 1c

FIG. 1.—Cushing's syndrome in Case 1. In Figs. 1a and 1b note the red cheeks, obesity and absence of striae, and in Fig. 1c the 'buffalo-hump' with hirsuties.

hair, but a small amount of pubic hair was present. There were no striae. The testes were in the scrotum and of normal size, as was the penis. The blood pressure was 150/95 mm. Hg.

PRINCIPAL INVESTIGATIONS. The serum cholesterol (average of seven estimations) was 325 mg./100 ml. (average for children is 150-200 mg./100 ml.).

An average of 10 estimations of eosinophils (Randolph method) gave 36 per c.mm.

For an insulin sensitivity test 3 units soluble insulin were given intravenously. The fasting blood sugar was 130 mg./100 ml., after half hour 84 mg./100 ml., after one hour 95 mg./100 ml., after one and a half hours 110 mg./100 ml. and after two hours 130 mg./100 ml. A high fasting blood sugar level and insulin resistance were demonstrated.

The radiographs of the skull showed a normal pituitary fossa, and of the skull, spine and pelvis well marked osteoporosis. The bone age was estimated to be seven years.

An intravenous pyelogram showed no abnormality and no abnormal extrarenal shadows.

The results of urinary steroid assays are set out in Tables 1 and 2. The 17-ketosteroids averaged about

TABLE 1
RESPONSE OF URINARY STEROID OUTPUT TO 9-ALPHA-FLUOROCORTISOL IN ROBERT

Day	Creatinine (g./24 hours)	17-Ketosteroids (mg./24 hours)	17-Hydroxycorticosteroids (mg./24 hours)	Amount of 9-Alpha-fluorocortisol Given (mg.)
1	0·51	6·8	21·7	Nil
2	0·56	7·1	20·9	2
3	0·54	7·7	17·4	2
4	0·58	9·3	16·2	5
5	0·54	6·8	16·4	5
6	0·33	3·5	8·0	5
7	0·28	3·6	9·1	Nil
8	0·32	2·7	11·9	Nil
9	0·32	2·7	9·6	Nil
10	0·33	4·1	12·1	Nil

TABLE 2
RESPONSE OF URINARY STEROID OUTPUT TO A.C.T.H IN ROBERT

Day	17-Ketosteroids (mg./24 hours)	17-Hydroxycorticosteroids (mg./24 hours)	Treatment with A.C.T.H. Gel (i.u. intramuscularly)
1	5·8	20·1	Nil
2	5·8	20·8	Nil
3	10·1	75·4	30×2
4	28·5	170·0	30×2
5	30·7	189·0	Nil
6	7·1	23·3	Nil

6 mg./24 hours (normal 1-3 mg./24 hours) and the 17-hydroxycorticosteroids were above 20 mg./24 hours (normal 2-4 mg./24 hours). Treatment by 9-alpha-fluorocortisol reduced the 17-ketosteroids to 2·7 mg./24 hours and the 17-hydroxycorticosteroids to 8·0 mg./24 hours. Treatment by A.C.T.H. gel (i.u. 30×2 daily for two days) increased the output of 17-ketosteroids to 30·7 mg./24 hours and the 17-hydroxycorticosteroids to 189 mg./24 hours.

One milligramme of phentolamine intravenously produced a fall in the systolic pressure from 160 mm. to 144 mm., which fall lasted less than one minute, and a fall in the diastolic pressure from 100 mm. to 80 mm. which lasted for one minute. This was interpreted as a negative result.

As a result of these investigations a diagnosis of Cushing's syndrome due to adrenocortical hyperplasia was made.

TREATMENT. It was decided to treat Robert by 9-alpha-fluorocortisol for a few months in view of the good suppression of adrenocortical activity achieved in a short test (Table 2). Adrenocortical suppression, however, was not obtained with doses as high as 19 mg. weekly and with this dosage the diastolic pressure rose to 120 mm. No difficulty arose from salt retention. When the failure of medical treatment was apparent surgical treatment was instituted. On September 25, 1956, seven-eighths of the left adrenal were removed by Mr. George Harrison (anaesthetist, Dr. Roger Bliss). Recovery was without incident. In the month after operation the 17-ketosteroids averaged 4·1 mg./24 hours and the 17-hydroxycorticosteroids 21·2 mg./24 hours.

On October 30, 1956, the right adrenal was completely removed and weighed 6 g. Intramuscular cortisone acetate was given 12 and two hours pre-operatively; during the operation, and for eight hours after, 75 mg. hydrocortisone were given by intravenous infusion. He was given diminishing doses of cortisone for 17 days after the operation, and for the next 25 days he was given no treatment. During this time he became noticeably less happy, and his red cheeks grew paler. He lost 1 lb. in weight and the 'buffalo hump' decreased in size. At the end of this time he began to vomit, and when the plasma electrolytes were at their lowest the chlorides were 97 mEq./1., sodium 128 mEq./1. and potassium 4.5 mEq./1. The urinary steroid and plasma cholesterol values were:

Post-Operative Day	17-Ketosteroids (mg./24 hours)	17-Hydroxycorticosteroids (mg./24 hours)	Cholesterol (mg./100 ml.)
28th	0·9	1·6	264
35th	1·3	1·5	158
42nd	1·2	<1	162

Since the fraction of adrenal cortex remaining was not being stimulated to activity by corticotrophin, and because an Addisonian crisis was threatening (blood pressure 94/70 mm. Hg), he was given maintenance therapy by cortisone and was discharged home for Christmas taking oral cortisone acetate, 12·5 mg. twice daily. He was readmitted a fortnight later with an acute tonsillitis which required vigorous treatment with increased doses of cortisone. He was discharged again with the same dose of cortisone and with prophylactic phenoxymethyl penicillin, 120 mg. twice daily, and 1 mg. of 9-alpha-fluorocortisol, twice weekly. During the 11 months of treatment and investigation he grew 1¼ in. in height.

In the nine months since his second operation he has grown more than 3½ in.

FIG. 2a.—Right adrenal (weight 6 g.).

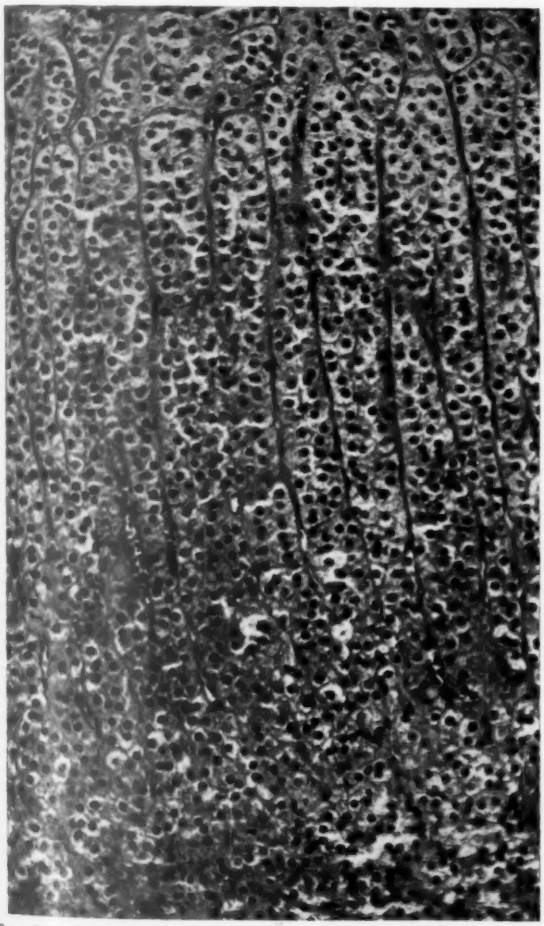


FIG. 2b.—Adrenal cortex × 150. Great hyperplasia of the zona reticularis, with diminution of the zona glomerulosa and disappearance of cholesterol in the zona fasciculata with the formation of compact cells.

HISTOLOGY. Dr. G. R. Osborn and Professor T. Symington reported as follows:

'In both adrenals (Figs. 2a and 2b) the zona glomerulosa is very inconspicuous, the zona fasciculata is present but fuses with a greatly enlarged zona reticularis with the compact cells growing into the zona fasciculata. Such changes are characteristic of adrenocortical hyperplasia resulting from stimulation by endogenous or exogenous A.C.T.H. (Symington, Duguid and Davidson, 1956). The medulla appeared to be normal.'

CONCLUSION. (1) The failure of growth in this boy was due to the excessive production of cortisol, which converts protein to glucose–gluconeogenesis. This is illustrated by the effect of 9-alpha-fluorocortisol on creatinine output; while reducing the output of the urinary 17-hydroxycorticosteroids from 21·7 mg./24 hours to 8 mg./24 hours, the urinary creatinine output was diminished from 510 mg./24 hours to 280 mg./24 hours (Table 1).

(2) The suppression of adrenocortical activity by 9-alpha-fluorocortisol indicated that this activity was dependent on endogenous A.C.T.H. stimulation (Cope and Harrison, 1955).

(3) The great enhancement of adrenocortical activity after exogenous A.C.T.H. stimulation indicated that the adrenal cortex was very sensitive to endogenous A.C.T.H. stimulation (Christy, Wallace and Jailer, 1955; Grumbach, Bongiovanni, Eberlein, van Wyk and Wilkins, 1955).

(4) These responses to A.C.T.H. and 9-alpha-fluorocortisol were taken to indicate that Robert was suffering from adrenocortical hyperplasia and not from an adrenocortical tumour.

(5) The depression of adrenocortical activity by 9-alpha-fluorocortisol during four months' treatment was inadequate for remission. A dose of 19 mg. weekly did not produce salt retention or oedema, but considerable hypertension, a result of the great cortisone-like activity of this substance. The higher the dose of 9-alpha-fluorocortisol the less salt retention it produces (Jailer,

TABLE 3

URINARY STEROID ASSAYS WEEKLY UNDER TREATMENT BY 9-ALPHA-FLUOROCORTISOL IN ROBERT

Week	17-Ketosteroids (mg./24 hours)	17-Hydroxycorticosteroids (mg./24 hours)	Amount of 9-Alpha-fluorocortisol Administered Each Week (mg.)
1	6·1	18·9	3
2	5·3	14·7	11
3	4·6	13·3	11
4	5·2	14·5	11
5	6·0	14·0	11
6	5·4	14·4	19
7	4·8	12·3	19
8	4·8	17·4	7
9	7·2	16·3	7
10	6·7	16·3	7
11	5·3	15·2	7
12	6·6	20·4	7
13	5·1	14·9	14
14	5·7	22·9	7
15	5·7	11·1	11
16	6·6	19·6	Nil
17	6·3	20·1	Nil
18	5·8	24·6	Nil

1956). This is unexplained. Phentolamine was used to test the hypothesis that cortisol, in some way, 'potentiates' the arteriolar constriction associated with the action of nor-adrenaline, but the intravenous injection of 1 mg. of phentolamine produced no significant fall of blood pressure. It was expected that the secretion of corticotrophin, originally depressed by 9-alpha-fluorocortisol, would eventually escape from its depressive effect, and so it proved (Table 3).

(6) No neoplasm was discovered at operation and the removed adrenal cortex showed hyperplasia of the zona reticularis.

Case 2. Helen was first seen by a surgeon at the age of 13 months on account of a large clitoris. The clitoris was noticed to be large at birth, and it had increased progressively in size.

She was an only child weighing 7 lb. 13 oz. at birth. The mother had toxaemia of pregnancy. There was no family history of intersex. The girl has developed normally, having learnt to sit without help at 6 months, to say single words with meaning at 10 months and to walk without help at 13 months. There had been no difficulty with micturition.

The clitoris was enlarged. The labia majora were normal. The labia minora were small. The urethral orifice was not localized. An intravenous pyelogram was normal. The results of studies in urinary excretion of 17-ketosteroids are shown in Table 4.

A year later, at the age of 25 months, she was seen again by the surgeon. The clitoris was enlarged, as before. It was now realized that the high figure for the 17-ketosteroids had been overlooked, and she was referred to one of us (R.S.I.).

TABLE 4

RESPONSE OF URINARY STEROID OUTPUT TO 9-ALPHA-FLUOROCORTISOL, TO PREDNISOLONE AND TO A.C.T.H. IN HELEN

Age in Months	17-Keto-steroids (mg./24 hours)	17-Hydroxy-cortico-steroids (mg./24 hours)	21-Deoxy-ketols (mg./24 hours)	Treatment
13	4·2			Nil
23	6·8			Nil
	5·6			Nil
28	7·6	19·5		Nil
	7·0	19·3		Nil
	6·7	14·3		9-*Alpha-fluorocortisol*
	—	—		0·25 mg. × 4
	2·3	6·1		0·25 mg. × 4
	3·8	11·1		Nil
	6·5	12·4		Nil
33	7·6	19·4	2·46	Nil
	7·2	18·1		Nil
				Prednisolone
	3·7	8·5		5 mg. × 2
	2·4	5·8		5 mg. × 2
	2·5	5·0		5 mg. × 2
	2·6	4·8	0·14	5 mg. × 2
	2·5	3·3		Nil
	6·8	17·5		Nil
	7·7	21·8	3·9	Nil
				A.C.T.H.
	10·7	32·5	7·20	20 i.u. i.m. ×2
	12·7	32·8		20 i.u. i.m. ×2
	15·2	53·2	8·57	20 i.u. i.m. × 1
	7·2	26·4	3·24	Nil
	2·6	20·4		Nil

FIG. 3.—Congenital virilism in Case 2 aged 2½ years.

On examination she was a bright, normal-looking girl (Fig. 3) speaking well in sentences. There had been no urinary incontinence after the age of 15 months. One was immediately impressed by the fact that she was of normal build, unlike other 'female pseudo-hermaphrodites'. Her height was 36 in.; the span from arm to arm was 35 in.; sitting height 20 in.; weight 26 lb. Her blood pressure was 100/70 mm. Hg.

The clitoris was considerably enlarged (Fig. 4) and there was chordee. The urethral orifice appeared to be on the anterior surface of the clitoris (Figs. 5a and b). There was no pubic hair. The vaginal orifice was normal. There was a diffuse functional grade 2 systolic murmur heard all over the praecordium. There were no other abnormal physical signs.

URINARY STEROID ASSAY. The results are set out in Table 4.

The 17-ketosteroids were approximately 7 mg./24 hours

FIG. 4.—Enlargement of the clitoris.

5a

5b

FIGS. 5a and 5b.—Urethral orifice in the clitoris and normally situated vaginal orifice.

and the 17-hydroxycorticosteroids were 19 mg./24 hours. Treatment by 9-alpha-fluorocortisol, 1 mg. daily for three days, reduced the 17-ketosteroids to 2·3 mg./24 hours, and the 17-hydroxycortisteroids to 6·1 mg./24 hours. Prednisolone (10 mg. daily for four days) reduced the 17-ketosteroids to 2·4 mg./24 hours and the 17-hydroxycorticosteroids to 3·3 mg./24 hours. A.C.T.H. gel, 20 i.u. twice daily for two and a half days, increased the 17-ketosteroids to 15·2 mg./24 hours and the 17-hydroxycorticosteroids to 53·2 mg./24 hours. The 21-deoxyketols were 2·46 mg./24 hours. (The normal excretion of 21-deoxyketols is very small, namely, 0·05-0·5 mg./24 hours in adults.) This level was reduced to 0·14 mg./24 hours by prednisolone and increased to 8·57 mg./24 hours by A.C.T.H.

Radiologically the epiphyseal development is as follows (the approximate age of the appearance of the epiphyses is given in brackets), and from these data the bone age may be regarded as approximately 4 to 5 years.

Bone	Epiphyseal Development.		
Arm and Hand			
Humerus ..	Head and tuberosites	(2 yr.)	present
	Medial epicondyle	(6 yr.)	present
Radius ..	Head	(6 yr.)	present
Ulna ..	Distal centre	(6 yr.)	absent
Carpus ..	Lunatum	(4 yr.)	absent
	Trapezium and scaphoid	(5 yr.)	absent
Femur ..	Great trochanter	(4 yr.)	present

A skin biopsy showed that Helen was a chromosomal female.

She has grown 1 in. in eight and a half months, and her height at the age of 2 years and 10 months is 37 in.

CONCLUSIONS. (1) This girl is suffering from congenital virilism as indicated by the enlarged phallus at birth. The increased output of urinary 17-ketosteroids indicated that this was associated with an excess of adrenal androgens, and the urinary output of 21-deoxyketols proves the presence of a defect in steroid synthesis which is characteristic of the adrenogenital syndrome.

(2) The suppression of the exaggerated adrenocortical activity by 9-alpha-fluorocortisol showed that this activity was dependent on endogenous A.C.T.H.; the brisk response to A.C.T.H. stimulation suggests that the hyperplastic adrenal cortex is sensitive to its action (Table 4).

(3) Her height is average for her age and her observed height increment is average or less; her bone age can be variously assessed at 3 years (carpus and hand) and 6 years (elbow), with an average epiphyseal development of 4 to 5 years. There is then a dissociation between the effect of the increased androgenic activity on height and its effect on skeletal development.

Discussion

Treatment of Cushing's Syndrome in Children. The complete removal in children of endocrine

FIG. 6.—Radiograph of the hand and carpus. The lunatum, trapezium and scaphoid and the distal epiphysis of the ulna are all absent. Bone age is 3 years.

glands which are essential for survival must always require careful consideration. Once the diagnosis of Cushing's syndrome is certainly established, and when it has been seen that the harmful consequences of the disease, such as failure of growth and hypertension, show no evidence of rapid remission, then bilateral total adrenalectomy becomes the treatment of election.

Replacement therapy demands subsequent regular medical supervision throughout life and in children both growth and the development of puberty require careful control of cortisone therapy. Any illness, accident or operation requires admission to hospital and increased cortisone dosage.

The alternatives to bilateral total adrenalectomy are subtotal adrenalectomy, which has been shown to be inefficient and which failed in Robert, and *x*-ray therapy to the pituitary. The application of *x* rays to the pituitary may be successful in temporarily depressing corticotrophin output, but its uncharted hazards to the growth and sex hormones make this a treatment to be avoided at least in children.

Pathogenesis of Cushing's Syndrome. A greatly enlarged zona reticularis was demonstrated in the adrenal cortex of Robert, and Symington and Grant (1957) have shown that this enlargement is associated with an increase of 11-β hydroxylase and that this hyperplasia can result from either increased endogenous or exogenous corticotrophin stimulation (Symington, *et al.*, 1956). There is a diminished amount of corticotrophin circulating in the plasma in Cushing's syndrome (Paris, Upson, Sprague, Salassa and Albert, 1954; Nelson, 1956) but there is an increased sensitivity of the adrenal cortex to exogenous A.C.T.H. (Grumbach *et al.*, 1955; Christy *et al.*, 1955). For some unexplained reason, therefore, in Cushing's syndrome (when it is not due to an adrenocortical tumour) the adrenal cortex becomes unduly sensitive to corticotrophin with a consequently increased production of cortisol. This hypothesis requires the assumption of some derangement of pituitary-cortex control, since the increased output of cortisol should, and apparently does, suppress the output of corticotrophin. It would be easy to assume that the adrenal cortex becomes entirely divorced from corticotrophin control, but it is difficult to understand, in that case, how Cushing's syndrome is relieved by *x*-ray therapy to the pituitary. To resolve this dilemma Jailer, Longson and Christy (1956) have deduced the presence of a 'corticotrophin-potentiating' hormone in the pituitary which is produced in excess in Cushing's syndrome. This attractive hypothesis awaits proof.

Diagnosis of the Adrenogenital Syndrome. In baby girls the recognition of this syndrome depends on the presence of an enlarged phallus, the persistence of the urogenital sinus, an advanced bone age, a raised output of urinary 17-ketosteroids and sometimes a salt-losing syndrome. In baby boys, when no genital abnormality calls attention to the condition, diagnosis may be very difficult.

In Helen, other diagnostic difficulties arose. The presence of an enlarged phallus at birth itself established the diagnosis of congenital virilism and the presence of an increased urinary output of 21-deoxyketols (which includes 17-alpha-hydroxypregnanolone but not pregnanetriol) established the fact that steroid formation in the adrenal cortex was abnormal. In this condition there is adrenocortical hyperplasia which has been attributed by Jailer, Gold, Vande Wiele and Lieberman (1949) and by Bartter, Albright, Forbes, Leaf, Dempsey and Carroll (1951) to the fact that there is a diminished formation of cortisol due to an enzymic defect in the adrenal cortex. The normal formation of

cortisol from progesterone gets as far as 17-alpha-hydroxyprogesterone (see Figs. 7a and b) and at some stage thereafter there is a block in the synthesis of cortisol. Since there is a reduced amount of cortisol produced there will be a reciprocal increase in corticotrophin production by the normal feedback mechanism. The increased amount of circulatory corticotrophin stimulates the adrenal cortex to the production of still further androgens, and virilism occurs. So much is agreed but beyond this there is debate and disagreement. Jailer *et al.* (1949) believe that the androgens are derived from 17-alpha-hydroxyprogesterone (a 21 carbon steroid) while Bartter *et al.* (1951) believe there is an excess of unidentified androgenic adrenal steroids. Dorfman (1956) believes that there are 19 carbon androgens which are not produced by a C21 pathway and are not, therefore, derived from precursors such as 17-alpha-hydroxyprogesterone. Bongiovanni and Eberlein (1956) have, however, shown that in the adrenocortical hyperplasia of congenital virilism there are 'respectable' quantities of steroid in the urine, which although not cortisol (Kendall's compound F (see Fig. 7b)) yet are C21 steroids which have an OH group at C10 and at C21. Reifenstein (1956) has recently reviewed this problem, which the steroid chemists have not yet solved.

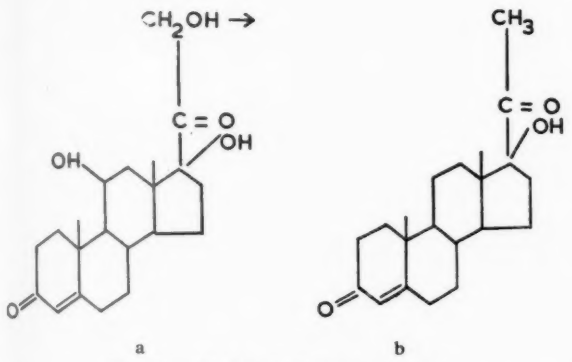


FIG. 7a.—17-alpha-hydroxyprogesterone.

FIG. 7b.—17-hydroxycortisone (cortisol) Kendall's Compound F.

Clinical problems also remain, and, in the absence of biochemical certainty, it is possible to construct a clinical hypothesis, as in the case of Helen, to explain them. It has already been observed that while Helen's height and her growth are both 'average' for her age, the excess of androgens has produced an enlarged phallus and a moderate advancement of the bone age (4-5 years). Before any endocrine assays were made it was assumed, according to a hormonal formula for growth (Hubble, 1957), that this dissociation could only be explained by the fact that the adrenal cortex in Helen was making a sufficient amount of cortisol to balance the excess of androgens, so that growth was proceeding at a normal pace.

Growth in childhood may be regarded as a competition for protein which is won by the protein anabolisers of which the most important is the growth hormone (G) with thyroxine (T) and insulin (I) in support; the opponent on the katabolic side of the formula is cortisol (C) which, disease and disaster apart, in childhood loses this struggle for protein, according to the formula

$$G+T+I > C.$$

At puberty and in the adrenogenital syndrome the androgens (A) come in to reinforce the protein-anabolic side of the formula and increased growth occurs

$$G+T+I+A > C.$$

In Cushing's syndrome, as in Robert, the excess of cortisol produced overcomes the protein anabolisers and growth is completely arrested.

$$G+T+I < C.$$

Since in Helen growth was at the same rate as in normal children, despite an excess of androgens, it was argued that an excess of cortisol was being produced to reduce the preponderance of the protein anabolisers. It has been shown that the production of 17-hydroxycorticosteroids in Helen's urine was in excess of normal, that they could be reduced to normal levels by 9-alpha-fluorohydrocortisone and that their output was nearly trebled by five intramuscular doses of 20 units of A.C.T.H. given in two and a half days. It was not possible to measure the plasma 17-hydroxycorticosteroids. The urinary 17-hydroxycorticosteroids include both the metabolites of compound F and of 17-alpha-hydroxyprogesterone, so it is not possible to say what amount of the 17-hydroxycorticosteroids was derived from cortisol breakdown. However, the urinary dihydroxyacetones which, with the triols, are the main normal metabolites of cortisol, were estimated in both these children on two occasions. In the boy with Cushing's syndrome they were 6·5 mg. and 3·4 mg. in 24 hours, and in the girl with congenital virilism they were 3·8 mg. and 2·2 mg. in 24 hours. It could be concluded, therefore, that the adrenal cortex in Helen was producing cortisol in average amounts.

Three out of 13 children suffering from the adrenogenital syndrome studied by Bongiovanni and Eberlein (1956) gave a response to intravenous A.C.T.H. in the level of plasma 17-hydroxycorticosteroids which was comparable with the normal. They concluded, therefore, that the defective synthesis of compound F is variable and not com-

plete. Clinical observation and chemical investigations are then agreed. One further possibility remains. The dihydroxyacetones might represent the breakdown products of 11-desoxycorticosterone (Fig. 8). Eberlein and Bongiovanni (1955) have

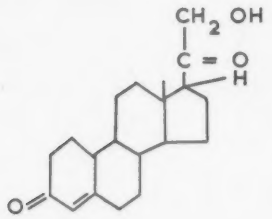


FIG. 8.—11-desoxycorticosterone.

described a rare variety of the adrenogenital syndrome accompanied by hypertension in which there is apparently a defect in 11-hydroxylation and they suggest that the hypertension is the result of the adrenal secretion of deoxycorticosterone. The urinary steroid assays in Helen do not preclude this possibility but there is as yet no evidence of hypertension in her.

Treatment of the Adrenogenital Syndrome. Cortisone was introduced in the treatment of congenital adrenal hyperplasia by Wilkins, Lewis, Klein, Gardner, Crigler, Rosemberg and Migeon (1951) and he and his collaborators have discussed the satisfactory results of such treatment in several papers (1956). The object of such therapy in girls is to reduce the masculinization which is a feature of the syndrome, to delay the advancement of epiphyseal development and to retard excessive growth so that the ultimate height may be that predestined by constitutional factors and not the stature determined by early closure of the epiphyses, and to permit the occurrence of the normal changes of puberty. All this is achieved by cortisone therapy.

In Helen the only present indication for such treatment is the moderate advancement of the bone age; the approach of puberty may make a reduction of androgen output advisable; the average height and the average annual height increments justify a period of observation before cortisone is used in treatment.

Conclusions

Two examples of adrenocortical hyperplasia have been described. In the boy Cushing's syndrome developed at the age of 6 years and declared itself by an arrest of growth. The disease was successfully treated by bilateral adrenalectomy.

In a girl aged 2½, congenital virilism due to adrenocortical hyperplasia has been described. In this child there is a dissociation between the effect of the increased formation of androgens on the phallus and on epiphyseal development and its effect on growth, which is proceeding in an average manner. It is suggested that a moderate amount of cortisol is being produced by the adrenal cortex and this is dependent on the fact that the defect in the synthesis of cortisol is only partial.

It is suggested that excessive growth is prevented in this girl by the balancing of the increased formation of androgens by the output of cortisol. This hypothesis is illustrated by the construction of a simple hormonal formula for growth.

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REFERENCES

Bartter, F. C., Albright, F., Forbes, A. P., Leaf, A., Dempsey, E. and Carroll, E. (1951). *J. clin. Invest.*, **30**, 237.
Bongiovanni, A. M. and Eberlein, W. R. (1956). *Adrenal Function in Infants and Children*, ed. L. I. Gardner, p. 76. New York and London.
Christy, N. P., Wallace, E. Z. and Jailer, J. W. (1955). *J. clin. Invest.*, **34**, 899.
Chute, A. L., Robinson, G. C. and Donohue, W. L. (1949). *J. Pediat.*, **34**, 20.
Cope, C. L. and Harrison, R. J. (1955). *Brit. med. J.*, **2**, 457.
Dorfman, R. I. (1956). In *Adrenal Function in Infants and Children*, ed. L. I. Gardner, p. 89. New York and London.
Eberlein, W. R. and Bongiovanni, A. M. (1955). *J. clin. Endocr.* **15**, 1531.
Grumbach, M. M. (1956). *Ibid.*, p. 99.
——, Bongiovanni, A. M., Eberlein, W. R., van Wyk, J. J. and Wilkins, L. (1955). *Bull. Johns Hopk. Hosp.*, **96**, 116.
Hubble, D. (1957). *Brit. med. J.*, **1**, 601.
Jailer, J. W. (1956). In *Adrenal Function in Infants and Children*, ed. L. I. Gardner, p. 102. New York and London.
——, Longson, D. and Christy, N. P. (1956). *J. clin. Endocr.*, **16**, 1276.
——, Gold, J. J., Vande Wiele, R. and Lieberman, S. (1949). *J. clin. Invest.*, **28**, 394.
Nelson, D. H. (1956). Quoted by Jailer, Longson and Christy (1956).
Paris, J., Upson, M., Sprague, R. G., Salassa, R. M. and Albert, A. (1954). *J. clin. Endocr.*, **14**, 597.
Reifenstein, E. C. Jr. (1956). *Ibid.*, **16**, 1262.
Symington, T. and Grant, J. K. (1957). In press.
——, Duguid, W. P. and Davidson, J. N. (1956). *Ibid.*, **16**, 580.
Wilkins, L. (1950). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence.* Springfield, Illinois.
—— (1956). In *Adrenal Function in Infants and Children*, ed. L. I. Gardner, p. 93. New York and London.
——, Lewis, R. A., Klein, R., Gardner, L. I., Crigler, J. F., Rosemberg, E. and Migeon, C. J. (1951). *J. clin. Endocr.*, **11**, 1.

AETIOLOGY OF CHOLELITHIASIS IN CHILDHOOD

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During the past 10 years case reports of cholelithiasis in childhood and adolescence have appeared fairly regularly and 24 cases under the age of 14 have been described in the English literature during this period. Though stated as being 'infrequent in early life' (Rapoport, 1954), most paediatricians must occasionally have found gall bladder disease to be the cause of hitherto unexplained abdominal pain.

Since 1940, nine cases of proved gall stones have been seen at The Hospital for Sick Children, Great Ormond Street, London. Stones are often associated with haemolytic anaemia, and two of the nine cases were found in association with erythroblastosis foetalis and have been reported by Lightwood and Bodian (1946). Three were found among 42 cases of classical acholuric jaundice, the biliary tracts having been examined in most of the 31 in which splenectomy was performed. Multiple stones were found in one girl who had a history of neonatal sepsis and in whom cavernomatous malformation of the portal vein with portal hypertension was found at the age of 7 years.

There is less awareness of the possibility of stones occurring in the absence of these conditions and, for this reason, the remaining three cases of gall stones of unusual aetiology are described in detail.

The records of 100 random cases of all types of haemolytic anaemia, representing most of the cases seen in this hospital since 1940, have been examined. The relative importance of haemolysis, infection and other aetiological factors is reviewed. The significance of pain as a symptom of gall bladder disease and the absence of splenomegaly in these cases is discussed.

Case Reports

Case 1. D.C., born August 27, 1952, an only boy of healthy parents, was born at term by spontaneous delivery (birth weight 7 lb. 2 oz.). His progress during infancy was uneventful and his developmental milestones were normal. Apart from very occasional vomiting he was well until the age of 3, when two weeks before admission he began complaining of periumbilical abdominal pain. Vomiting relieved the pain and, at this stage, he was slightly constipated. Four days before admission, he became tired, anorexic and listless and had a bout of severe pain lasting three hours. Two days later he passed a slightly pale stool and again complained of pain. During the week before admission his urine at times appeared darker than usual.

On examination on December 28, 1955, he looked unwell, slightly dehydrated and possibly icteric. He was pale with flushed cheeks and a few scattered recent bruises on the shins were seen. He had minimal faucial congestion. The abdomen was scaphoid and the liver edge was palpable at the umbilicus, smooth, firm and tender. There was a slightly nodular feel at one point along its edge on one occasion during his first admission.

The results of the initial investigations included a haemoglobin which was 85% (12·58 g. per 100 ml.), the white blood cell count was normal and the sedimentation rate 11 mm. in one hour. The urine showed a slight trace of protein, no deposit and a positive reaction for bile pigments and salts. The total serum bilirubin was 0·7 units per 100 ml.; the thymol turbidity, 1 unit; Kunkel turbidity, 1 unit; alkaline phosphatase, 26 units per 100 ml.; total serum proteins (drop method), 6·1 g. per 100 ml. with diminished γ globulin on electrophoresis. His glucose tolerance curve, blood urea and stool culture were normal. Radiographs of the skull, long bones, chest and abdomen were normal though some opacities on the right side of the abdomen were seen. After further films they were considered to be artefacts.

With bed rest and symptomatic treatment he improved, regaining his appetite and gaining weight within a few days. On January 3, 1956, six days after admission, the urine bile pigments and salts had disappeared and the alkaline phosphatase level on January 10 was 15 units per 100 ml. He was discharged home on January 20 on a reduced fat diet, a provisional diagnosis of infectious hepatitis having been made.

On February 27 he was readmitted after a recurrence of severe abdominal pain, having been well since discharge except for a four-day attack of gastro-enteritis. Again the liver edge was almost down to the umbilicus and the fullness at its edge suggested an enlarged gall bladder. The Fouchet test for bilirubin in the urine was initially negative and became positive three days after admission for five days. The serum bilirubin reached 1·2 g. per 100 ml. and other blood and urine investigations (including serum cholesterol) showed no significant change. Cholecystography on two occasions showed

normal gall bladder and biliary duct shadows. No calculi were visualized. As before, the abdominal pains gradually settled and on discharge on April 6 the liver edge was 1-1½ in. below the costal margin.

On June 18 the boy was readmitted having had a recurrence of symptoms and the liver, having been normal in size during follow-up as an out-patient, had again enlarged to half-way between the costal margin and the umbilicus. He had gained only 8 oz. since the previous admission. The liver function tests were as follows: Serum bilirubin (total) less than 0·5 mg. per 100 ml., alkaline phosphatase 14 units per 100 ml., thymol and Kunkel turbidities 9 and 7 units respectively, total serum proteins 5·8 g. per 100 ml., the greatest reduction being in globulins, especially γ globulin. The red blood cell fragility was normal and the reticulocyte count was 0·8%.

A laparotomy was performed by Mr. H. H. Nixon on July 4 when a cholecystectomy was performed and a liver biopsy was taken. The post-operative course was uneventful and he was discharged symptom-free on the eleventh post-operative day. The turbidity tests were normal before discharge though the γ globulin was still reduced on electrophoresis. When seen one month after discharge he was symptom-free though his weight gain was still slow.

Laparotomy material was examined. The gall stone was mainly organic. Cholesterol and bilirubin were detected, but no phosphate, calcium or carbonate. The gall bladder showed myohypertrophy of the bladder wall.

The architecture of the liver and the hepatic cells were normal. There was moderate infiltration of the sinusoidal vessels and to a lesser extent of the portal areas with polymorphonuclear leucocytes, probably an inflammatory sequel to intermittent obstruction of the bile ducts.

Serial sections of the cystic duct showed it to be patent throughout its length and there was no evidence of any stenosis.

Case 2. J.W., born on July 29, 1942, an only girl of healthy parents, was born after a normal pregnancy and labour (birth weight 7 lb. 14 oz.). Her development was normal during infancy and she had measles, whooping cough and recurrent tonsillitis with cough and vomiting in her early years. Her tonsils and adenoids were removed in 1948 (aged 6 years), but it was not till a year later she attended The Hospital for Sick Children, Great Ormond Street. In May, 1949, she was seen on account of kyphoscoliosis and was given physiotherapy. She began to complain of attacks of fever associated with dysuria, frequency and nocturnal enuresis. She was treated at home successfully with a sulphonamide preparation. In June (one month later) after some physiotherapy the fever, this time of 102° F., recurred and she developed headache and anorexia. She had pain over the right iliac crest for four days when it suddenly disappeared.

On examination she was found to be in good general condition but had a throat infection. A soft, insignificant cardiac murmur was heard and no other abnormality was found. Radiographs of the spine showed slight scoliosis and although there were a few W.B.C.s and a scanty growth of *Esch. coli* was obtained from a catheter specimen of urine it was alkaline and contained no protein. She was therefore referred back to her home doctor with recommendations for chemotherapy.

She next attended in October, 1951, with complaints of fatigue, lassitude, night sweats, rare 'bilious attacks' and occasional aching across the shoulders. These had been present intermittently for about two years. Re-examination showed a slightly tender right hypochondrium with a liver edge ½ in. below the costal margin.

The Mantoux test (1:100) was positive, the E.S.R. was 12 mm. in one hour, the chest radiograph was clear but the spine radiograph showed the persistence of scoliosis and suggested the presence of at least two gall stones. Cholecystography proved that the opacities were within the gall bladder (Fig. 1). Further investigations before cholecystectomy gave the following results: Blood group O Rh positive; Hb 96% (13·4 g. per 100 ml.); R.B.C. count 4·98 million (reticulocytes 0·4%); red cells on a blood film appeared normal and red cell fragility was normal; W.B.C. count 6,200 per c.mm. (46% neutrophils, 54% lymphocytes); platelet count 277,860 per c.mm.; total serum bilirubin 0·29 mg. per 100 ml. (all of direct type); blood cholesterol 149 mg. per 100 ml.; urine normal.

Cholecystectomy was performed by Mr. Macnab on November 26, 1951. One month later she was doing well and was discharged from the Surgical Department to continue physiotherapy for poor posture and scoliosis.

Laparotomy material was examimed. The gall stones contained 1·4% cholesterol and the bilirubin test was strongly positive.

Bile culture was sterile.

The gall bladder was macroscopically and microscopically normal.

Serial sections of the cystic duct showed that there was undoubtedly very severe stenosis of a segment of the cystic duct, but no complete atresia. A lumen, however small in one area, seemed to be present throughout.

Case 3. C.S., born on June 18, 1943, the second child (female) of healthy parents was born spontaneously at term (birth weight 9 lb. 14 oz.). The neonatal condition was satisfactory and there was no jaundice. Breast feeding ceased at 2 weeks owing to failure of lactation, but apart from excessive lacrimation of the left eye, her progress was satisfactory until December, 1943. She was then admitted to hospital with a 10-week history of vomiting and pale, hard stools and an eight-week history of jaundice. The urine was bright yellow though this and the jaundice were becoming less intense before admission. The appetite had been good and she was gaining weight. There had been no contact with infectious hepatitis and no source of homologous serum jaundice was found. Her 16-year-old brother was normal.

On examination she was fretful and febrile (temp. 102°). Despite the history she was about 1½ lb. under her expected weight. She was moderately jaundiced and not obviously anaemic. The abdomen was distended, the liver was two fingerbreadths below the costal margin but the spleen was not felt. There were no other significant findings.

The Hb was 103%, the W.B.C. count was 13,000 per c.mm. with a normal differential count. No microspherocytes were present. The urine contained bile, and the stool was colourless, dry and crumbly. The total serum bilirubin was 6·2 mg. %, the Takata-Ara reaction was negative and the R.B.C. fragility was normal. A chest radiograph was normal and the Mantoux test (1:1,000) was negative.

Three days after admission shifting dullness was detected in the abdomen and on December 19, with the temperature, pulse and respiration gradually rising, abdominal paracentesis yielded thick, dark, bile-stained fluid. The treatment to date consisted of sedatives and intramuscular vitamin K. Shortly after the paracentesis her condition deteriorated rapidly and she died the same day.

NECROPSY. There was deep jaundice. The abdomen was distended and thick, purulent, bile-stained fluid was found in the peritoneal cavity. There was fibrinous exudate over the bile-stained, distended intestines. The liver was large, deeply jaundiced but otherwise normal. The gall bladder was empty but a stone was found at the junction of the hepatic and cystic ducts. It appeared that the infection seen in the bile passages had given rise to general peritonitis. The spleen was small and bile-stained. The stomach was distended and contained coagulated and coffee-ground material. The meninges were congested and multiple punctate haemorrhages were seen in the cerebral white matter. The other viscera were normal apart from the presence of jaundice.

It was concluded that the common bile duct had been obstructed by gall stone (probably pigment stone) causing obstructive jaundice, and secondary acute inflammation of the bile passages leading to staphylococcal peritonitis.

Aetiology

Age. The first report of gall stones in infancy is stated by Snyder, Chaffin and Oettinger (1952) to have been made in 1767. In 1899 Still reviewed 20 case reports and added three further cases in infants under the age of 9 months. The calculi in Still's patients were very small and often numerous. They resemble those described by Lightwood and Bodian (1946) in two children under 6 months of age with erythroblastosis foetalis. It was not until later that stones were observed in the foetus. Still (1899) considered it likely that the stones in some of his cases were formed during intra-uterine life and Jones (1951) reported a case associated with intra-uterine cholecystitis. Snyder *et al.* had, by 1952, found only two other reports of stones in the foetus, but had collected 90 cases in infancy in the world literature.

Although before puberty gall stones are commoner than cholecystitis (Ladd and Gross, 1941) they nevertheless occur infrequently (Rapoport, 1954). The commonest associated feature in this age period is the haemolysis of acholuric jaundice in the white and of sickle cell anaemia in the coloured races. Mintz, Church and Adams (1955) go so far as to say that if stones occur under the age of 40 years in a coloured patient he should be examined for sickle cell anaemia, though Weens (1945) narrows the age range, stating that stones associated with this type of anaemia are seldom seen in the first decade.

Sex. Robertson (1945) in an historical review on the subject of gall stones states that in adults over 30 years of age females are affected twice as often as males. Ulin, Nosal and Martin (1951) also found a female preponderance in gall bladder stones associated with cholecystitis in children. Forshall and Rickham (1954) reported stones in five children with abnormalities of the biliary ducts and they were all females. In general, the female proneness to gall stones seems less marked in childhood and in the present series there were five females and four males. The two cases of erythroblastosis were males, the child with portal vein changes following neonatal sepsis was a female, two of the three with acholuric jaundice were females, that with cystic duct stenosis was female and there was one of each sex of unknown cause.

Race. There is an obvious racial selection related to the incidence of the various haemolytic anaemias discussed below. But in addition Ansari (1953) points out that gall stones are rarer in India than in western Europe, England or the United States. The incidence of stones within the white races varies considerably from place to place within a geographical area as well as from one region to another. There must be dietetic and environmental factors yet unrecognized which play a part in this geographical selection.

Haemolytic Anaemia. For many years the association between gall stones and acholuric jaundice has been recognized and now sickle cell anaemia is incriminated. As might be expected the incidence of stones is greater in adult life, the Mayo Clinic figure in congenital haemolytic anaemia quoted by Mintz *et al.* (1955) being 70%. Gross (1953) found gall stones in three out of six children under 14 years of age with haemolytic anaemia.

TABLE 1
ANALYSIS OF 100 CASES OF HAEMOLYTIC ANAEMIA

	Acholuric Jaundice	Erythroblastosis Foetalis	Atypical Haemolytic Anaemia	Acute (Lederer) Haemolytic Anaemia	Thalassaemia	Sickle Cell Anaemia
Number	42	29	16	6	6	1
Gall stones found	3	2	—	—	—	—
Abdominal pain present	14	—	5	2	1	—
Pain referrable to gall bladder	6	—	1	1	—	—
Spleen not palpable	1	9	2	4	1	—
Splenectomy	31	—	4	—	1	—

In the present series five out of nine children had haemolytic disease. These five were found on analysis of 100 cases of haemolytic anaemia covering the period 1940-56 (Table 1).

Cholecystitis. Ladd and Gross (1941) state that in children gall stones are commoner than cholecystitis. With the control of typhoid and scarlet fevers and of upper respiratory tract infection this is probably true though study of the literature would suggest that this has not always been the case. The association between the two is accepted and cases have been reported recently by Lawler, West and Murphy (1951), Ulin *et al.* (1951), Dannenberg and Sarioglu (1954) and others. Lawler *et al.* (1951) surprisingly state that stone formation is not often a sequel of infection, yet Potter (1938) calculated that 27·9% and Ulin *et al.* (1951) 68% of cases of cholecystitis in children had calculi. There is agreement, however, that common bile duct stone is rare; 6% is the figure given by Ulin *et al.* (1951) and less than 3% by Potter (1938) and Pratt, Sauer and Gray (1951). In the presence of long-standing disease it may be difficult to decide whether the stone or the inflammation was primary. In the nine cases in this series none were regarded as being due to primary cholecystitis.

Anatomical Anomalies. Perhaps too little attention has been paid to the possibility that macroscopic or microscopic abnormalities of the bile duct system could be the primary cause of obstruction leading to stagnation and stone formation. Forshall and Rickham (1954) report four cases in which minor anatomical abnormalities were responsible, and similar findings are recorded by Bogatko and Mehlman (1947), Liège and Musac (1951) and at the Paediatric Clinical Conference (1949). Vague reference is made to such abnormalities by Lawler *et al.* (1951) and there are a number of other cases in which such changes might be suspected, but in which serial sections of the cystic duct were not reported. This examination was done in retrospect in two of the three cases presented here and in Case 2 a segmental stenosis was found. In cases without other obvious aetiology this detailed histology is certainly justified and may prove rewarding. Cystic duct obstruction caused by the cystic lymph gland has been recorded on two occasions (Jones, 1951; Rankin, 1955). In one, this caused acute distension of the gall bladder and in the other gall stones and acute cholecystitis were found.

Miscellaneous Factors. The importance of dehydration in the presence of partial or complete obstruction of the biliary tract is obvious, but other mechanisms have been suggested to account for the occurrence of stones in the absence of infection or obstruction. Tesler (1946) suggests that genetic as well as constitutional factors are at work because he found gall stones in identical twins. Sodeman (1950) points out that absence of bile salts causes precipitation of cholesterol and Dannenberg and Sarioglu (1954) suggest that agglutinins may cause bile precipitation round which a stone could form. Rankin (1955), in describing acute distension of the gall bladder, suggests 'biliary dyschezia' as a cause. If such a condition exists it could obviously play a part in the production of stones.

Symptoms and Diagnosis

The classical story of right subcostal pain, the finding of tenderness and possibly enlargement of the gall bladder and finally the visualization of gall stones radiologically makes for easy diagnosis. Despite the confidence of Babbitt (1956) it is very apparent from the literature and from two of the three cases described that these symptoms and signs are not infrequently wanting. Nausea, vomiting and jaundice can be caused by other conditions, the pain is often vaguely situated and may localize in the right iliac fossa (Walker, 1951) and back and shoulder pain are rare (Ladd and Gross, 1951; Forshall and Rickham, 1954).

Jaundice as a symptom of gall bladder stones is a surprisingly frequent finding in spite of the low

incidence of common duct obstruction (Potter, 1938). Alternative suggestions as to the mechanism of obstruction include pressure on the common duct by the gall bladder itself or hepatocellular damage.

The frequency of an impalpable spleen in haemolytic anaemia is recorded in Table 1. Splenomegaly is a reliable sign in cases with prolonged or recurrent haemolysis and its absence might be expected in acute haemolytic episodes. Thirty-four per cent. of babies with erythroblastosis were found to have impalpable spleens. The size of the spleen is no help in the diagnosis of gall stones due to haemolytic disease.

The incidence of abdominal pain was investigated in the 100 cases of haemolytic anaemia outlined in Table 1. Of the 14 cases of acholuric jaundice with abdominal pain, in only six was the pain related to the gall bladder area. Of 16 children with atypical haemolytic anaemias and six with acute Lederer type, five and two cases respectively had pain. This was related to the gall bladder area only once in each instance. The pain may in some of these cases, as in the child with thalassaemia, be due to the immense size of the spleen but this could not have been the cause in many. It is probable that gall stones are responsible for the pains in some of the cases of long-standing haemolytic anaemia; the fact, however, that pain may occur after cholecystectomy (Weens, 1945; Mintz *et al.*, 1955) led these authors to suggest alternative causes such as hepatic or mesenteric infarcts, splenic haemorrhages or nerve root pain due to vertebral changes. The pain can be mistaken for appendicitis (Lawler *et al.*, 1951; Liège and Muzac, 1951; Walker, 1951); and Hirsch and Freedland (1953) found appendicitis, cholecystitis and multiple stones in the one patient. The diagnosis is more difficult when the stones are not visualized by straight radiography or cholecystography. Despite the warning of Ulin *et al.* (1951) recurrent hepatitis was diagnosed in my Case 1 and Bogatko and Mehlman (1947) made initial diagnoses of hepatitis and pancreatic cyst in the light of negative radiography. As in Case 1 laparotomy is the ultimate necessity in these difficult cases and most writers agree that this should not be delayed unduly. At the same time they recall to mind the risks of operation in the presence of hepatic disease. Occasionally a normally functioning gall bladder containing stones may be left *in situ* if the stones are considered small enough to be passed spontaneously (Babbitt, 1956).

Although it is unlikely that 'silent' stones occur as often as in adults (50% or more are silent, Robertson, 1945; Horn, 1956) it is probable that quite a number of infants with rhesus incompatibility have small stones. It is even more likely that more of the cases of acholuric jaundice and sickle cell anaemia with or without pain have stones, especially as one of the three cases of acholuric jaundice mentioned above had entirely symptomless stones. No other record of such a case was found, though this is perhaps not so surprising in view of the earlier splenectomy now performed in this condition. Babbitt (1956) describes two cases in which fair-sized radiologically positive stones remained 'silent' for some months before producing typical features.

Summary and Conclusions

During the period 1940-56, nine proved cases of gall stones have occurred in The Hospital for Sick Children, Great Ormond Street. Two were associated with erythroblastosis foetalis and three with acholuric jaundice. One was of a girl who had neonatal sepsis and later was found to have cavernomatous malformation of the portal vein and portal hypertension. The remaining three, one of segmental stenosis of the cystic duct and two of unknown aetiology, are described fully.

The diagnosis and management of these cases is described and discussed.

I wish to thank the Medical Committee of The Hospital for Sick Children for granting access to the notes of the cases reviewed and in particular to Dr. G. H. Newns for his help and advice, to Dr. Martin Bodian and his staff for their valuable assistance and special reports on Cases 1 and 2 and to Miss Wright and Miss Crawford for their secretarial help.

References

Ansari, M. Y. (1953). *Indian J. Pediat.*, **20**, 119.
Babbitt, D. P. (1956). *Amer. J. Dis. Child.*, **92**, 5.
Bogatko, F. H. and Mehlman, J. (1947). *J. Pediat.*, **31**, 75.
Dannenberg, A. M. and Sarioglu, A. R. (1954). *Amer. J. Dis. Child.*, **88**, 350.
Forshall, I. and Rickham, P. P. (1954). *Brit. J. Surg.*, **42**, 161.
Gross, R. E. (1953). *The Surgery of Infancy and Childhood*, p. 531. Philadelphia.
Hirsch, H., Ray, E. B. and Freedland, M. E. (1953). *Calif. Med.*, **79**, 318.
Horn, G. (1956). *Brit. med. J.*, **2**, 732.
Jones, R. N. (1951). *Lancet*, **1**, 324.
Ladd, W. E. and Gross, R. E. (1941). *Abdominal Surgery of Infancy and Childhood*, p. 287. Philadelphia.
Lawler, R. H., West, J. W. and Murphy, R. P. (1951). *Amer. J. Surg.*, **81**, 421.
Liège, R. and Muzac (1951). *Arch. franç. Pédiat.*, **8**, 98.
Lightwood, R. and Bodian, M. (1946). *Archives of Disease in Childhood*, **21**, 209.
Mintz, A. A., Church, G. and Adams, E. D. (1955). *J. Pediat.*, **47**, 171.
Paediatric Clinical Conference (1949). *J. Pediat.*, **34**, 777.
Potter, A. H. (1938). *Surg. Gynec. Obstet.*, **66**, 604.
Pratt, G. F., Sauer, W. G. and Gray, H. K. (1951). *Gastroenterology*, **18**, 443.
Rankin, W. (1955). *Archives of Disease in Childhood*, **30**, 60.
Rapoport, M. (1954). In *Textbook of Pediatrics*, ed. Nelson, W. E. 6th ed., p. 744. Philadelphia.
Robertson, H. E. (1945). *Gastroenterology*, **5**, 345.
Snyder, W. H., Chaffin, L. and Oettinger, L. (1952). *J. Amer. med. Ass.*, **149**, 1645.
Sodeman, W. A. (1950). *Pathologic Physiology*, p. 342. Philadelphia.
Still, G. F. (1899). *Trans. Path. Soc. Lond.*, **50**, 151.
Tesler, J. (1946). *Gastroenterology*, **7**, 685.
Ulin, A. W., Nosal, J. L. and Martin, W. L. (1951). *J. Amer. med. Ass.*, **147**, 1443.
Walker, P. A. (1951). *Brit. med. J.*, **1**, 1242.
Weens, H. S. (1945). *Ann intern. Med.*, **22**, 182.

THE ELECTRON MICROSCOPY OF ENDOCARDIAL FIBROELASTOSIS*

BY

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It has been shown (Still and Boult. 1956) that when teased preparations of the endocardium in congenital endocardial fibroelastosis are studied by electronmicroscopy the superficial zones are largely composed of a material bearing little resemblance to collagen or elastic tissue, as the histological appearances suggest, but having the morphological characters of fibrin. We proposed therefore that this material's presence must be due to the incorporation of surface deposits into the endocardium.

Teased preparations cannot, however, represent accurately either the exact position of fibres, or their relative amount in the endocardium, and only thin sections can do this satisfactorily. A study of such sections is described in this communication, and it seems to bear out our previous conclusions.

Material and Methods

The left ventricular endocardium from seven infants aged 6 to 9 months with diffuse endocardial fibroelastosis were examined. From each heart a 1 mm. cubed block of endocardium from the surface area was taken (Fig. 1). The blocks were treated with 1% buffered osmic acid as an electron stain, and embedded in a mixture of butyl and methyl metacrylate. The blocks were sectioned on a Cook and Perkins ultramicrotome with a heat-expanding object arm, and in general the sections used for viewing were in the region of 300 to 400 A° in thickness (10,000 A° = 1 μ). Photographs were taken at magnifications of between 6,000 and 9,000 times and enlarged photographically.

Controls

Before examining the pathological endocardium by electron microscopy, it was necessary for comparison to ascertain the appearances of collagen, elastic tissue and fibrin in ultra-thin sections. Fig. 2 is a thin section of a child's aorta, in which collagen and elastic tissue are shown. The collagen is seen as clearly defined individual fibrils about 800 to 900 A° wide and showing periodic cross striations at 640 A° intervals. The elastic tissue is represented by the wide dark-staining band, with no apparent periodic cross striation or fibrillary pattern. These appearances are not essentially different from what is seen in our own teased preparations and moreover they answer to the recognized description of collagen and elastic tissue (Gross and Schmitt, 1948; Hall, Reed and Tunbridge, 1955).

The electron microscopic appearances of fibrin, in teased form, have been defined by Hawn and Porter

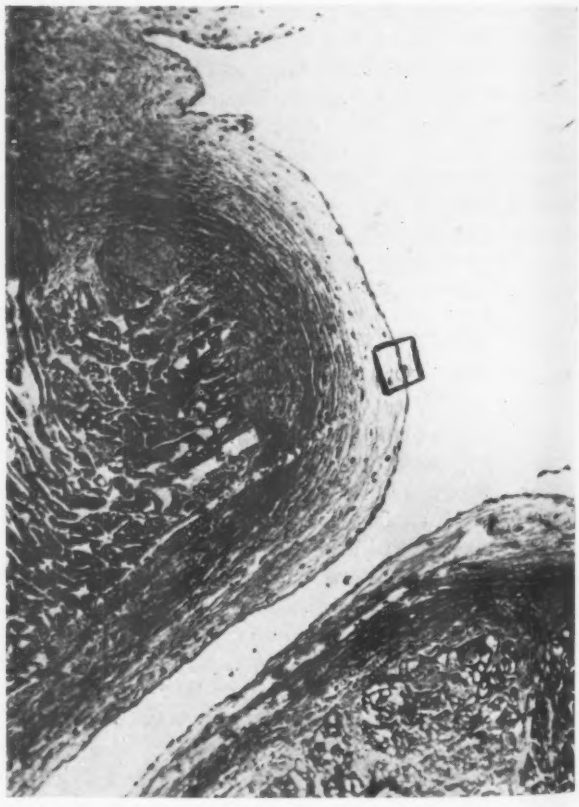

FIG. 1.—Paraffin section of endocardium. The area investigated by electron microscope is marked thus □. Haematoxylin and eosin. × 125.

* Read at a conference of the Pathological Society of Great Britain in January, 1957.

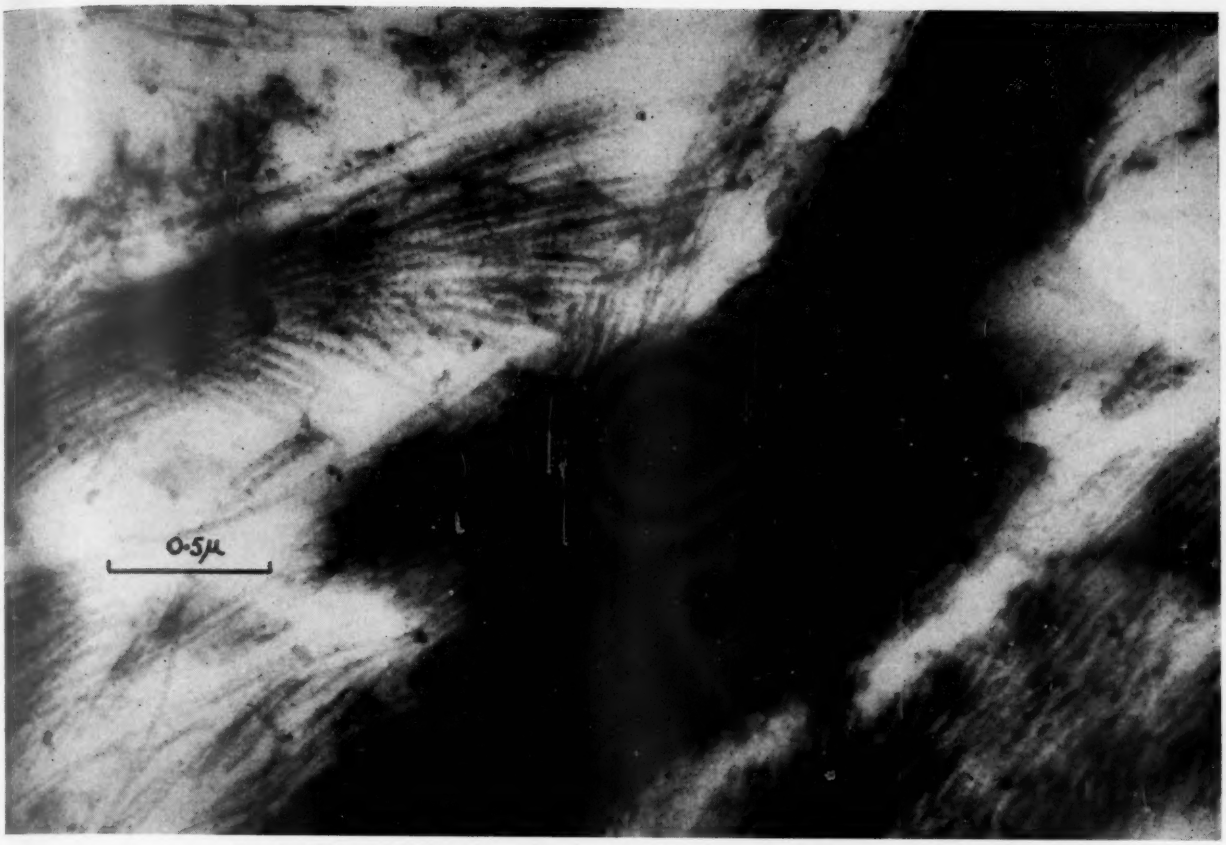

FIG. 2.—Thin section of child's aorta, showing collagen and elastic tissue. × 30,000.

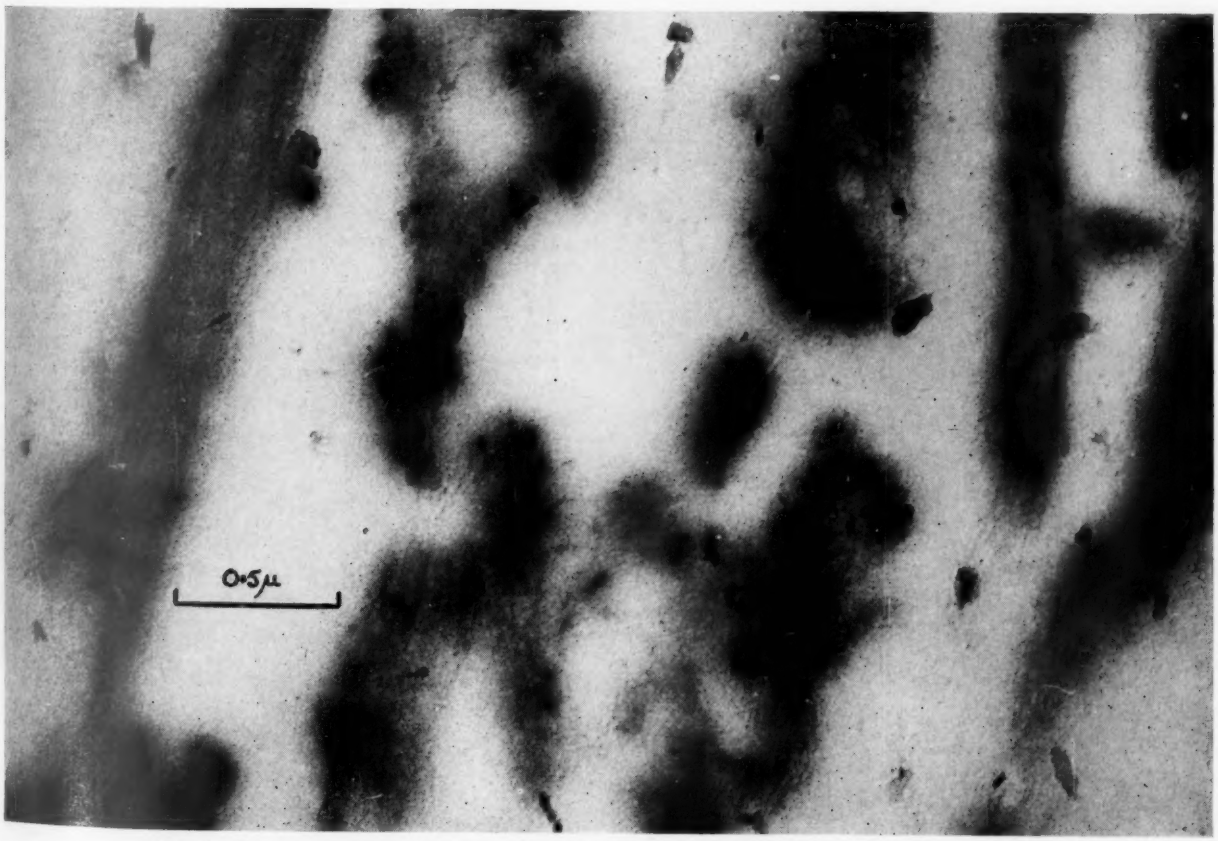

FIG. 3.—Common appearance of known fibrin in a thin section of inflammatory exudate. × 45,000.

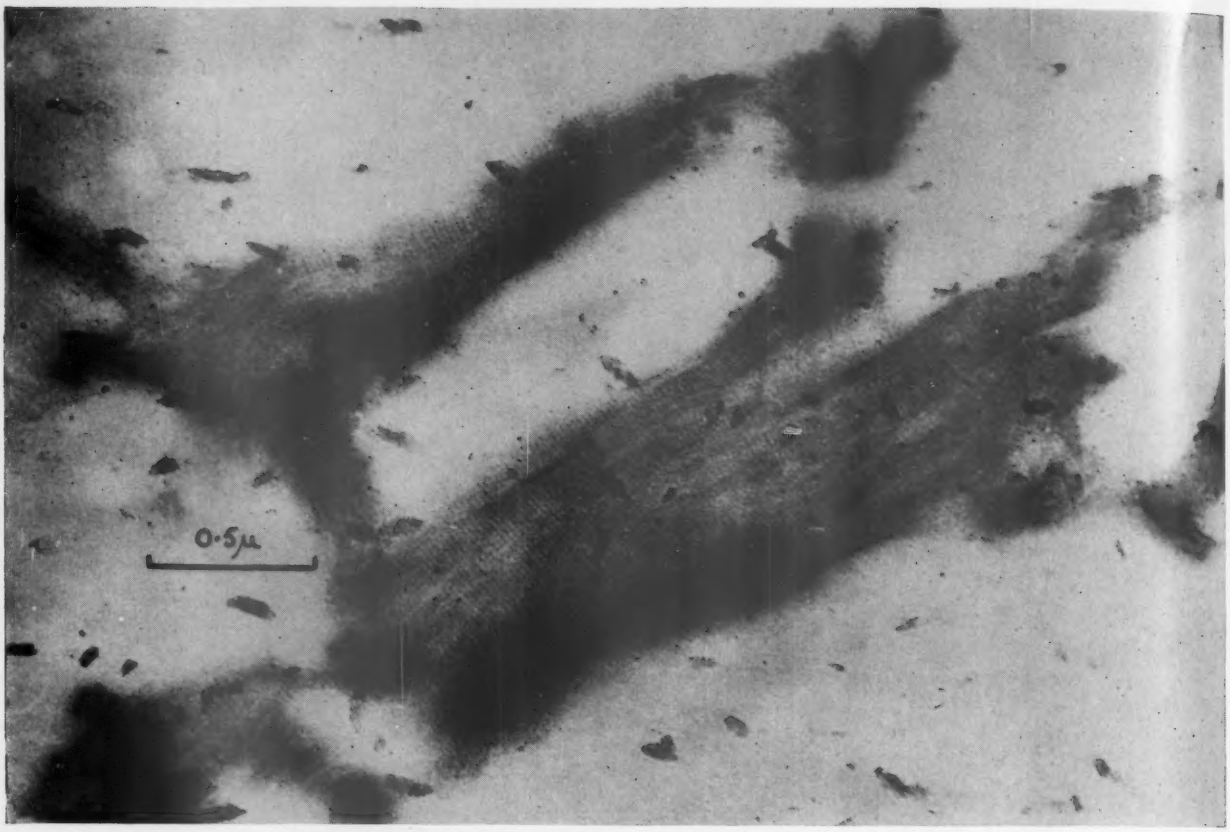

FIG. 4.—Striated appearance of fibrin from inflammatory exudate. × 45,000.

FIG. 5.—Fibrillary material from subendothelial layer of endocardium. See Fig. 3. × 45,000.

FIG. 6.—Fibrillary material from subendothelial layer. Endothelial cell at top left hand corner. × 15,000.

FIG. 7.—Higher magnification of material in Fig. 6. Cross striation at 230 A° intervals present (see Fig. 4). × 45,500.

FIG. 8.—Sheet of fibrillary material from subendothelial layer. See Figs. 3 and 5. × 45,000.

(1947) and Hall (1949). The fibrin fibril, about 100 to 150 A° wide, has characteristic periodic cross striations at about 230 A° intervals. Fibrin in ultra-thin sections, however, presents apparently two appearances. Fig. 3 shows the common appearance of fibrin in a thin section from an inflammatory pericardial exudate; the fibrin fibrils, about 200 A° wide, are arranged in small bundles, but there is little or no periodic cross striation to be seen. Fig. 4 shows what is in our experience a relatively uncommon appearance of fibrin, where the periodic cross striations at 230 A° are clearly marked, but no clear fibrillary pattern is present.

Results

Sectioning of the endocardium from the cases of endocardial fibroelastosis showed that of the seven examples, four contained, in their superficial layers, material bearing a close resemblance to fibrin as seen in the controls. Two others showed in this area material which, although not directly comparable with fibrin, was unlike either elastic tissue or collagen.

Fig. 5, for example, shows material from the subendothelial zone. Here the material is fibrillary and the individual fibrils are, as far as can be judged, about 200 A° wide, and arranged in bundles, but no definite periodic cross striations are present. Figs. 6 and 7 are from the same region in another case. In them, slender branching bundles of fibrillary material are seen just deep to an endothelial cell in the top left hand corner. This material shows both the recognized criteria of fibrin; parts are of a fine fibrillary nature and others show a well marked periodic cross striation at about 230 A° intervals. The latter areas present a close resemblance to the banded appearance of known fibrin as seen in Fig. 4.

In two specimens of endocardium a slightly different type of fibrillary material was found just under the endothelium. This (Fig. 8) is composed of a relatively large sheet of thin (200 A°) fibrils lying more or less in parallel with no apparent cross striations. They do, however, bear some resemblance to the individual fibrils of fibrin as seen in Fig. 3 and are unlike collagen fibrils, some of which are seen incidentally in the corner of the section. Sectioning of the endocardium showed that the

fibrous material we have described was confined to an area just beneath the endothelial cells and it did not appear to be present in the main body of the endocardium, which was composed of collagen and elastic tissue only.

Discussion

Histologically, the endocardium in endocardial fibroelastosis, including the superficial zones, only gives the staining reactions of collagen and elastic tissue, but electron microscopy shows that at least one other type of fibrous material is present. In this communication and in a previous one, we have put forward the idea that this material may be fibrin, or its derivative, which has become incorporated into the endocardium after surface deposition. Thin sections indicate that the material is situated under the endothelium and that it bears a close resemblance to acknowledged fibrin. The section technique brings out two other points: first, that although the material is less abundant than the teased preparation seemed to suggest, it is still present in considerable amounts, and secondly, that the material is in the form of discrete masses rather than as a continuous layer.

The comparisons we have made are purely morphological, and on these grounds alone we cannot be certain of the identity of the material, but it is clear that it bears little or no resemblance to either collagen or elastic tissue.

Summary

The endocardium in endocardial fibroelastosis was studied by electron microscopic thin sections. It was found that the fibrillary material just deep to the endothelium resembled fibrin and was dissimilar to both collagen and elastic tissue. This confirmed the results of teased preparation studies.

We wish to thank Professor J. B. Duguid for advice and criticism and Miss Barbara Harris for preparing the enlargements.

References

Gross, J. and Schmitt, F. O. (1948). *J. exp. Med.*, **88**, 555.
Hall, C. E. (1949). *J. biol. Chem.*, **179**, 857.
Hall, D. A., Reed, R. and Tunbridge, R. E. (1955). *Exp. Cell Res.*, **8**, 35.
Hawn, G. V. Z. and Porter, K. R. (1947). *J. exyp. Med.*, **86**, 285.
Still, W. J. S. and Boult, E. H. (1956). *Lancet*, **2**, 117.

HYPOPHOSPHATASIA

BY

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The purpose of this paper is to describe the histological findings in two cases of congenital hypophosphatasia. Of the two cases, the second was diagnosed only in retrospect and without biochemical confirmation.

In 1948 Rathbun described a generalized disease of bone which was associated with hypophosphatasia, hypercalcaemia and a renal lesion. To this he gave the name 'hypophosphatasia'. Since then other cases have been reported under various names both here and abroad (Engfeldt and Zetterström, 1954; McCance, Fairweather, Barrett and Morrison, 1956; Schlesinger, Luder and Bodian, 1955). From the cases described it is possible to build up a composite clinical picture of this rather bizarre condition. The usual presenting feature is a failure to thrive in the early months of life associated with vomiting and constipation. Biochemically the most significant finding is the virtual absence of the enzyme alkaline phosphatase. In addition there is hypercalcaemia, and renal damage has been found at necropsy providing yet another condition associated with renal calcinosis.

Rathbun's case differs from others so far recorded in the literature in being much younger. The age at death of his patient was 2 months. This may be the explanation of the clinical finding of an almost uncalcified skull. He described the head of this infant as resembling a balloon filled with water. It was this description which suggested the diagnosis in the first of the two cases about to be described.

Case Reports

Case 1. This was a boy, born of healthy parents and with two healthy older siblings. After an uneventful pregnancy the child was delivered by low forceps under general anaesthesia. He was cyanosed at birth but this cleared within a few minutes. Thereafter he had repeated cyanotic attacks and vomited the sugar and water which he was given. When seen on the second day of life the most striking feature was the apparent absence of bone in the vault of the skull. Small plaques of bone could be felt in the occipital and frontal regions, while the rest of the cranium felt like the water-filled balloon described by Rathbun. The spleen was palpable one fingerbreadth below the costal margin and the liver two fingerbreadths. No other abnormality was found on clinical examination. The child was admitted to the Royal Hospital for Sick Children, Glasgow, on the second day of life. He had repeated convulsions poorly controlled by sedatives and died at the age of 15 days.

X-RAY APPEARANCES. There was defective ossification of the skull and delayed dentition (Fig. 1). The ribs were flared at the costochondral junctions. The metaphyses of the long bones were irregular and pathological fractures of the shafts with some stippling of the epiphyses were observed.

BIOCHEMICAL FINDINGS. The serum calcium level was 18·5 mg./100 ml.; alkaline phosphatase, less than 1·5 K-A units/ml. (three estimations); non-protein nitrogen, 55 mg./100 ml. Post-mortem estimation of

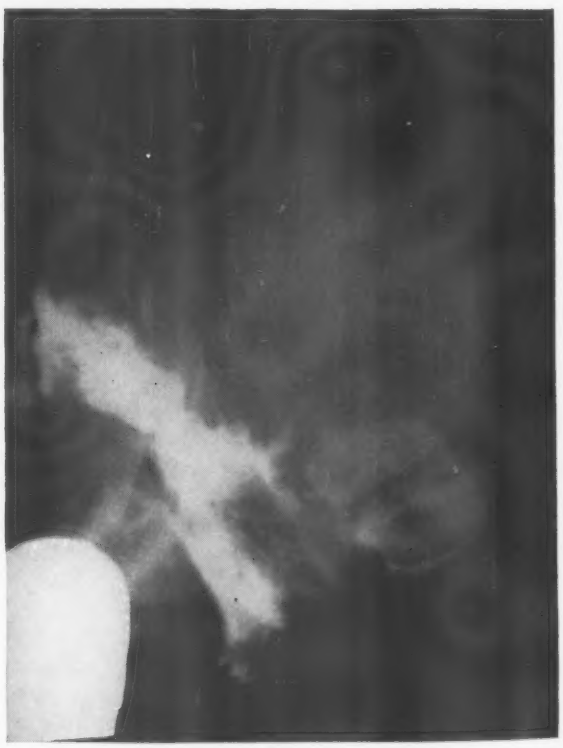

FIG. 1.—Case 1: Radiograph of the skull showing defective calcification.

alkaline phosphatase in the lower end of a humerus yielded 140 K-A units/kg. The average recorded range in the absence of obvious bone disease, and depending upon the site and activity of the growing bone, is 580 to 12,000 K-A units/kg. (Rathbun, 1948).

Necropsy. The body was of average development for a 15-day-old infant and weighed 3·1 kg.

HEAD. The skull felt soft over the vertex, and when the skin was reflected the parietal bones, the posterior aspect of the frontal bones and the anterior aspect of the occipital bones were cut easily with scissors. The base of the skull and the mandible appeared normal. The brain which, weighed 423 g., was removed and sectioned; no lesion was recognized. The venous sinuses were normal.

THORAX. The thoracic contents showed no abnormality. The thoracic cage, however, presented abnormalities at the costochondral junction of the third to tenth ribs on each side. The end of the bone was broadened with an apparent excess of cartilage giving a swollen, wrinkled junction over 1·5 cm., thereafter becoming the normal flattened cartilage articulating with the sternum which itself was normal. The vertebral bodies were smaller than usual but of normal shape. The heads of the ribs were normal. The thyroid gland and paratracheal tissue were carefully dissected and no evidence of parathyroid enlargement was seen.

ABDOMEN. The abdominal contents were substantially normal: in particular, no renal lesion was recognized.

Histology. The lungs, heart, trachea, thyroid, parathyroid, salivary glands, pancreas, spleen, pituitary and testes were examined and showed no significant departure from the normal. An occasional small cast was seen in the cortical tubules of the kidney but no histological evidence of disease was recognized.

THE SKELETON. The following bones were taken for histological examination: ribs, humerus, radius, ulna, femur, tibia, fibula, lumbar vertebra and frontal bone. All blocks were decalcified by the ion-exchange resin method, cut and stained by the picro-Mallory method. All showed lesions, varying only in extent with the individual bone, and the most remarkable were found in the ribs. Here the picture was a grossly distorted metaphyseal line with complete loss of alignment of the columns of cartilage and an irregular pattern of osteoid deposition. Next to the osteoid, a band of bone ran across the rib with another zone of osteoid on the shaft side (Fig. 2). All the ribs examined showed this general picture. Under higher magnification the main features identified were those of a rachitic lesion, namely, the excessive osteoid formation, the development of compression of the cartilage cells at the cartilage-shaft junction and the invasion of the cartilage by capillary loops. The main feature, however, which distinguished this lesion from that of active rickets was the band of bone between the layers of osteoid.

By contrast, an example of a minimal and presumably early lesion could be obtained from an examination of the distal end of the fibula (Fig. 4). Here the metaphysis was abnormally broad and the cartilage dipped into the shaft at irregular intervals. The osteoid was increased in amount and deposition of bone was variable. Evidence of early compression of cartilage cells could be seen.

The lesion was not always observed throughout the breadth of the metaphysis. As in the upper end of the femur on the medial aspect (Fig. 6), it was often local. In the bones examined this type of local lesion was always subcortical in position. The remainder of the metaphysis was normal as was the spongiosa.

In normal controls of the same age the proportion of osteoid to bone was found to be variable, the most constant feature being the regularity of the alignment of the spongiosa. Thus in both the grades of lesion described the spongy bone of the shaft was uninformative except in that the spicules of spongy bone in the ribs examined were much thicker and better ossified than in the normal controls. This is in contrast to the picture seen in active rickets.

Similar lesions were found at the lower ends of both femur and fibula. In addition, the fibula showed a lesion which was confined to the shaft (Fig. 5). Here a band of osteoid and poorly calcified bone traversed the shaft about 15 mm. from the metaphysis. This appeared to be a healing fracture and the deficiency of cortical bone at this point strongly suggested an intra-uterine origin.

Even at this early age of 15 days, evidence of some healing could be found. Such an example was seen in the head of the radius (Fig. 3) where there was bone deposition on irregular columns of cartilage cells. As in rickets the phases of osteoid production and ossification may thus occur together. There were, however, some examples also of broadening of the cartilage with no attempt at ossification as in the distal end of the ulna. Thus repair lacked uniformity and varied with the individual bone. A lumbar vertebra was examined and bone formation found to be within normal limits.

At a higher magnification it can be shown that in normal controls the osteoblastic reaction does not surround every spicule and that even where bone is being laid down most actively, namely, near the metaphysis, the presence of osteoblasts is inconstant. Thus an evaluation of osteoblastic activity can only be made by examining a considerable extent of bone. In the ribs of this case there was no doubt about the presence of osteoblasts around some of the osteoid at the metaphysis (Fig. 7). Osteoblastic activity was also demonstrable in the bone scar and the adjacent cartilage (Fig. 2). Periosteal deposition of bone was active as estimated by the number of osteoblasts (Fig. 8), where there was also an excessive deposition of osteoid. Osteoclasts were very seldom found in association with the spongiosa although they were occasionally seen in periosteal bone.

Even in the mild lesion as in the lower end of a fibula, the irregularity of bone deposition on the spongiosa was clearly demonstrable, while the osteoblastic reaction round these spicules was within normal limits. Where the bone had fractured the osteoblastic response was good and evidence of bone modelling was recognized by the occasional presence of osteoclasts. In the fracture of the lower end of fibula the osteoid was young and

FIG. 2.—Case 1: Rib, picro-Mallory × 12.

FIG. 4.—Case 1: Fibula, picro-Mallory × 12.

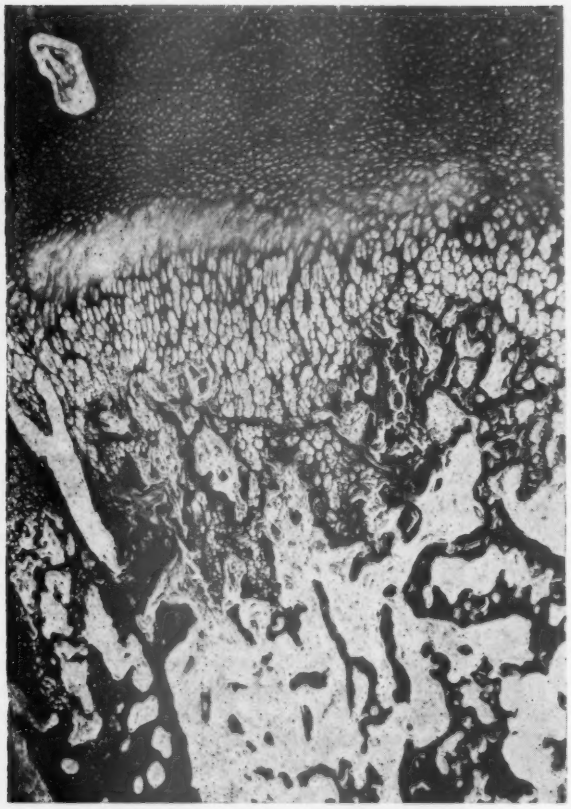

FIG. 3.—Case 1: Radius, picro-Mallory × 22.

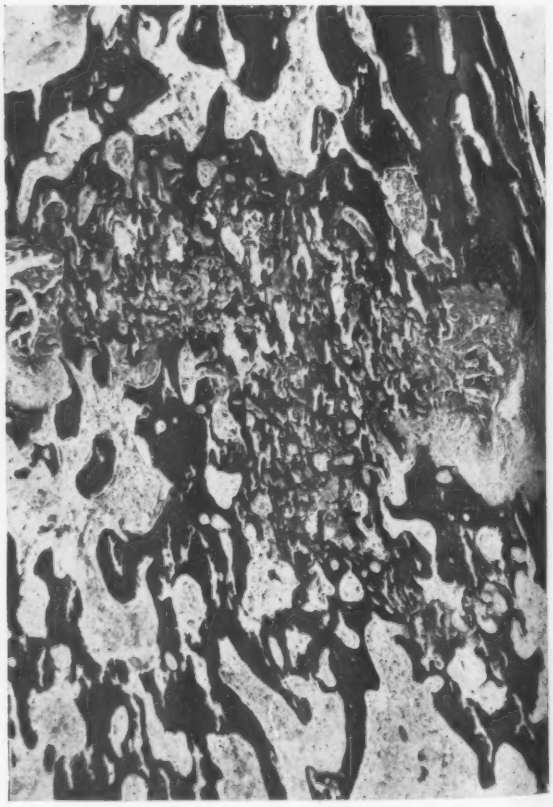

FIG. 5.—Case 1: Fibula, picro-Mallory × 22.

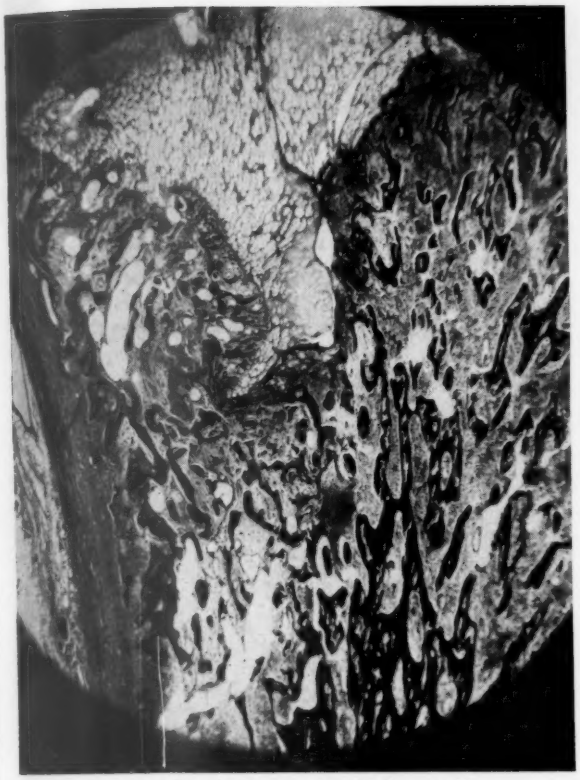

FIG. 6.—Case 1: Femur, picro-Mallory × 12.

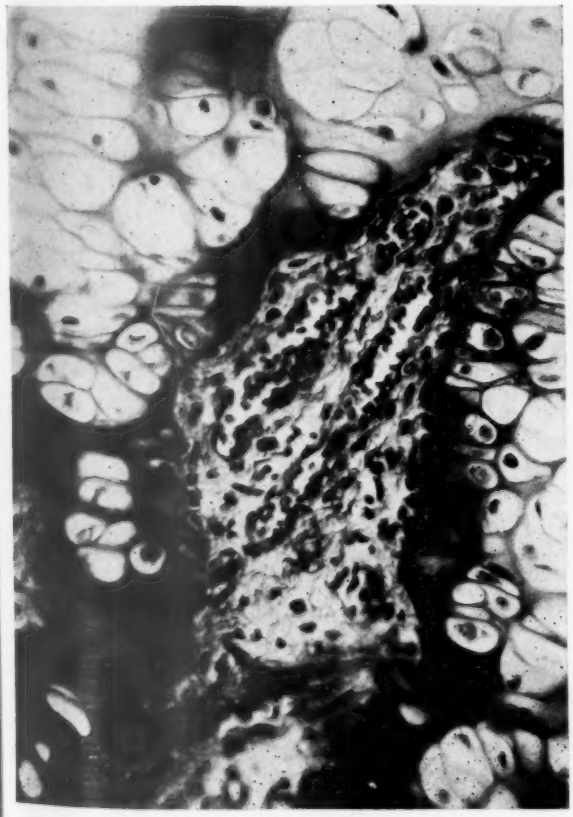

FIG. 7.—Case 1: Rib, picro-Mallory × 260.

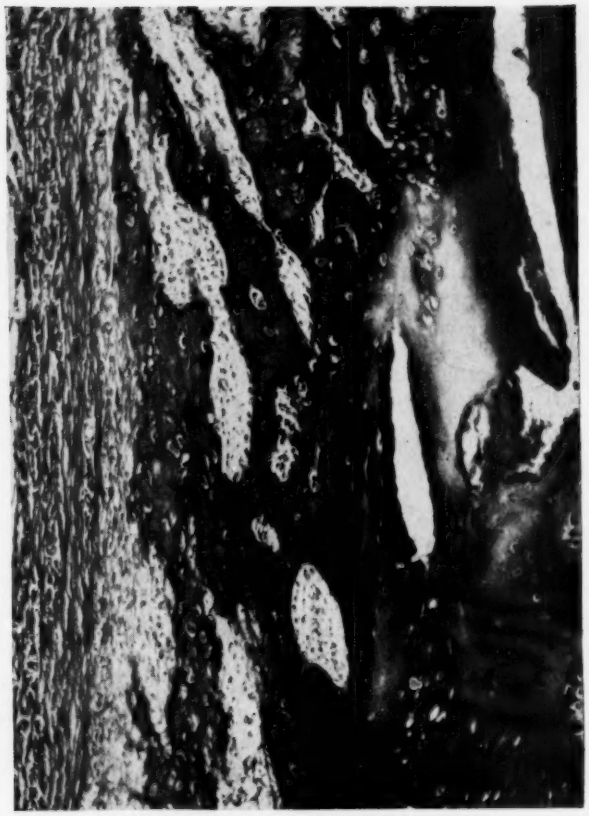

FIG. 8.—Case 1: Rib, picro-Mallory × 95.

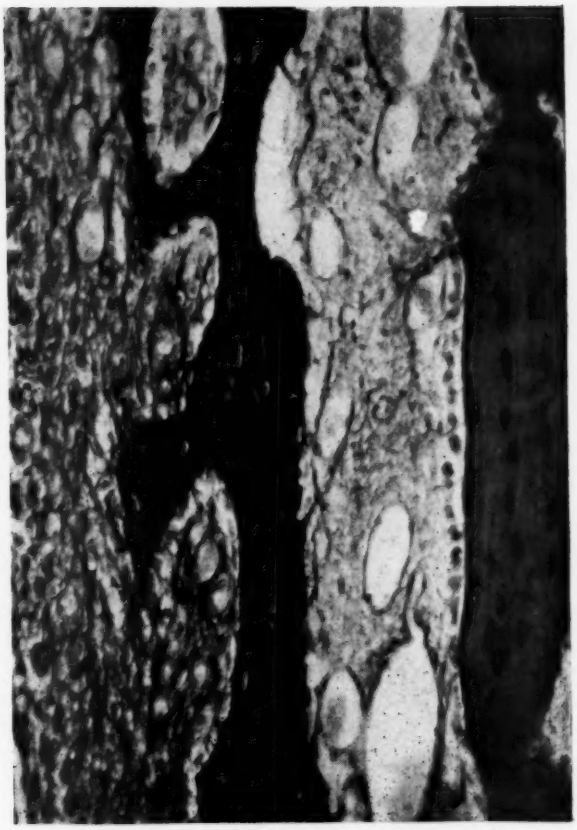

FIG. 9.—Case 1: Parietal bone, picro-Mallory × 180.

more actively laid down in the spongiosa than in the cortex, where there was actually a gap in the bone (Fig. 5). At the head of the radius where the metaphyseal lesion was more advanced in repair than in any other bone examined, the osteoblastic activity was good. Here again there was a slight increase in connective tissue.

Osteoblastic activity was more marked in the calvarium than in any bone examined. The outer table was poorly ossified but the inner table was more normal in density. It would appear that the defect is in the actual deposition of calcium. Certainly all the cellular components were present (Fig. 9) and the architecture of the membranous bone was within normal limits.

Case 2. This was a boy, born of healthy parents. He was the fifth child in the family and only one other child survived. In one, who had died almost immediately after birth, the diagnosis of achondroplasia had been made elsewhere. The history of the present case was that he appeared healthy at birth but after the first month he vomited intermittently, took his feeds poorly and failed to thrive. At the age of 6 weeks he was found to have widespread bony deformities and the skull sutures were widely separated. At this time a diagnosis of polyostotic dysplasia was made. He was first admitted at the age of 6 months with acute diarrhoea and vomiting and died the following day before any investigations could be carried out.

X-RAY APPEARANCES. In the light of new information the films of this child who died in 1950 were re-assessed by Dr. S. P. Rawson who suggested a revised diagnosis of hypophosphatasia.

FIG. 12.—Case 2: Kidney, Von Kossa × 4½.

SKULL. There was deficient mineralization of bones forming the vault of the skull with wide sutures and enlargement of the fontanelles. The base of the skull was also affected to a lesser degree.

LONG BONES. There was deficient mineralization with abnormal patchy calcification of the metaphyses which show irregular zones of proliferative cartilage, enlargement of the epiphyses and an increase in width of the epiphyseal cartilage. The long bones were bowed from deficient bone structure.

RIBS. There was some decalcification with expansion and flaring at the outer ends at the costochondral junctions.

Necropsy. The body was that of a rather thin male infant weighing 3·4 kg., this being only half his expected weight. The upper and lower limbs were misshapen, in that they were bowed outwards and were shorter than the average. The bones of all four limbs were removed and examined.

SKULL. The fontanelle was large and the frontal bones were not as well ossified as one would expect at this age.

ALIMENTARY SYSTEM. There was nothing of note apart from a considerable fatty change in the liver.

GENITO-URINARY SYSTEM. The left kidney weighed 33 g. and the right 30 g. Both organs were congested, the medulla more so than the cortex. At the boundary zone of the medulla were numerous streaks of a crystalline deposit: these proved to be calcium (Fig. 12). Pelvis, ureters and bladder were normal.

THORAX. The contents of the thoracic cavity revealed no abnormality of note.

Histology. The lungs, heart, pancreas, spleen, adrenal, pituitary, cerebellar cortex, cerebral cortex and marrow were examined and showed no significant lesion.

LIVER. There was moderate fatty change with considerable intracellular pigment in the periphery of the lobule.

THYMUS. Some small centres of erythropoiesis were seen in the septa.

ILEUM AND COLON. There was lymphoid hyperplasia with some infiltration of inflammatory cells into the villi, indicating a degree of enteritis.

KIDNEY. Each kidney showed a considerable degree of medullary calcinosis with a few small focal lesions in the cortex as well. The medullary lesions consisted of discrete granulomatous patches with granular degeneration, variable in size and characteristically situated in the outer medullary zone. The patches contained a variable amount of calcium stainable by Von Kossa's method (Fig. 12). One may presume that these would obstruct the tubules and cause subsequent dilatation. The granulomata probably originate both in and between the tubules.

The histological picture conforms to the description of nephrocalcinosis by Rhaney and Mitchell (1956).

SKELETON. The following bones were available for examination: humerus, radius, ulna, tibia, fibula and both femora. All showed a similar lesion. At the distal end of the right tibia (Fig. 10), the thickened line of cartilage was clearly seen and into this grew loops of capillaries, a feature indistinguishable from rickets. Equally evident was the broad line of densely ossified cancellous bone on the shaft side of the capillary loops. This band was constant at the ends of all long bones examined. At a higher magnification (Fig. 11) the collapse of columns of cartilage cells could be seen between the invading capillary loops. Osteoblasts were numerous. Their presence was most marked at the cortex and in the band of bone next to the metaphysis where osteoclasts were also seen. The spicules of the spongiosa were smaller than normal so that for some distance on the shaft side of the dense metaphyseal band the medullary bone was more rarified (Fig. 10). Nevertheless the ossification within the shaft was normal. There seemed to be little attempt at bone modelling here as osteoclasts were scanty.

FIG. 10.—Case 2: Tibia, picro-Mallory × 4.

FIG. 11.—Case 2: Tibia, picro-Mallory × 12.

Discussion

The diagnosis of the first case can hardly be called in question; apart from the close clinical resemblance to Rathbun's case, the extremely low figures for alkaline phosphatase both in blood and bone must be regarded as conclusive. The diagnosis of the second case, on the other hand, must remain to some extent presumptive. Nevertheless the clinical and radiological picture is sufficiently close to make such a diagnosis a reasonable assumption. To add to this there is a similarity in the histological appearances of the bones of both these cases which outweighs the differences, especially as the latter may well be due to the difference between their ages at death.

The radiological picture itself is sufficiently distinctive to suggest the diagnosis. The combination of multiple fractures and grossly defective ossification of the skull is highly suggestive; indeed the picture shown of the skull in our first case (Fig. 1) is probably pathognomonic.

In assessing histological deviations from the normal we have kept in mind the possible variation which may be found unassociated with disease. For this reason a number of samples of ribs at the costochondral junction were examined from children of

the age of 14 days who had died from causes not related to bone disease or disorder of calcium metabolism as far as was known. It was apparent that at this age there was considerable variation in the extent of the ossification of the spongiosa and of the osteoblastic activity associated with it. The normal regularity of the metaphyseal line, however, was constant.

Samples of other generalized disorders of bone were also examined for purposes of comparison. The features of osteogenesis imperfecta and achondroplasia differed so considerably from our own two cases that detailed comparison is unnecessary.

Classical rickets presented more of a problem. In the first place, other writers have used the term rickets for this disease as it affects the older child in whom metaphyseal changes are radiologically more marked while changes in the skull are less (Schlesinger *et al.*, 1955).

Secondly, whereas a fair comparison might be made between classical rickets and our second case, this was not possible in the case of an infant only 2 weeks old. Nevertheless, in both cases some of the salient features of rickets were apparent. There was broadening of the metaphysis with an increase in osteoid tissue and irregular bone formation, invasion of the cartilage by capillary loops and compression of the columns of cartilage cells (Park, 1939). The differences are, perhaps, more remarkable than the similarities. Most noteworthy is the presence of the metaphyseal band of bone running through the osteoid seen in our cases. Moreover, and this is seen most markedly in our second case which might otherwise be regarded as more closely resembling rickets, there is the combination in the same section of signs of activity (invasion of capillary loops) and signs of healing (bone formation). Minor differences from rickets are the multiple spontaneous fractures, the rarity of osteoclasts, and the well-ossified spicules of the spongiosa.

In this connexion it must be remembered that in any specialized tissue the possible reaction to disease must inevitably be limited by its structure. It is likely, therefore, that any interference with the normal ossification process of the growing bone will result in a somewhat similar histological picture. There are already described various kinds of rickets such as renal rickets, resistant rickets and others with causes ranging far from the original concept of a vitamin deficiency. On this analogy it might well be possible to include hypophosphatasia as yet one more example of 'rickets'. There is a danger, however, in degrading the term 'rickets' with its relatively clear-cut pathogenesis into a generalization including all disorders of ossification. The advantage of the term hypophosphatasia lies in its emphasis upon an important diagnostic feature and moreover brings it into line with the current concept of familial enzymatic deficiencies to which the disease probably belongs (McCance *et al.*, 1956).

It remains to consider the term 'osteoblastic dysplasia' introduced by Schlesinger and his colleagues (1955). In neither of our cases could such a view be sustained; the variability of osteoblastic activity in the normal was found to be such that the usual bone biopsy must be regarded as inadequate for its assessment.

The presence of nephrocalcinosis in a condition associated with hypercalcaemia is not unexpected. It is tempting to see its gradual development during the course of the disease at different ages. In our first case dying at the age of 2 weeks there was no obvious renal damage. In Rathbun's case dying at 2 months there was a renal lesion without calcinosis, while in our second case dying at the age of 6 months the complete lesion of medullary nephrocalcinosis could be demonstrated.

Summary and Conclusions

Two cases of congenital hypophosphatasia are described, the second case being a presumptive diagnosis based upon clinical, radiological and post-mortem findings. Detailed histological examination of the skeletons in both cases showed many of the histological features of rickets. Nevertheless, the whole picture differs considerably from that disease. Some of the clinical and radiological variations described in the literature are probably associated with the differing ages at death of the cases described. No evidence was found for regarding hypophosphatasia as an osteoblastic deficiency.

We are grateful to Professor Stanley Graham and Dr. J. H. Hutchison, O.B.E., for permission to report these cases, to Dr. H. E. C. Wilson and his staff for the biochemical reports and to Dr. S. P. Rawson for the *x*-ray reports.

References

Engfeldt, B. and Zetterström, R. (1954). *J. Pediat.*, **45**, 125.
McCance, R. A., Fairweather, D. V. I., Barrett, A. M. and Morrison, A. B. (1956). *Quart. J. Med.*, **25**, 523.
Park, E. A. (1939). *Harvey Lect.*, Ser. 34, p. 157.
Rathbun, J. C. (1948). *Amer. J. Dis. Child.*, **75**, 822.
Rhaney, K. and Mitchell, R. G. (1956). *Lancet*, **1**, 1028.
Schlesinger, B., Luder, J. and Bodian, M. (1955). *Archives of Disease in Childhood*, **30**, 265.

PROTEIN-BOUND IODINE LEVELS IN MOTHERS AND INFANTS AT BIRTH

BY

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The protein-bound iodine level in the blood is important in relation to thyroid gland activity.

Various aspects of blood iodine are discussed by Samson Wright (1952). Iodine is present in the blood in the hormone form of thyroxine and diiodotyrosine bound with albumin and precipitated out with the serum proteins, the protein-bound or precipitable iodine; the normal range of this hormone iodine is 3·5 to 8 μg. per 100 ml.

Kennedy and Hayles (1948) mention that protein-bound iodine levels may be raised to values of 10 to 12 μg. per 100 ml. during pregnancy and in early infancy.

Iodine is also found in the blood as inorganic iodide or filterable iodine, the level of which is dependent on iodine intake; this is not related to thyroid gland activity as is the protein-bound iodine. In patients with hypothyroidism the protein-bound iodine levels are reduced; in hyperthyroidism the level is raised.

The present report represents a study to determine normal levels of protein-bound iodine in the serum of mothers taken within an hour of the delivery of an infant and the levels in the serum of umbilical cord blood of their infants taken immediately after delivery. The protein-bound iodine was determined by the method of Connor, Swenson, Park, Gangloff, Lieberman and Curtis (1949) as modified by Van Zyl (1953). Table 1 presents the

TABLE 1
OBSTETRIC HISTORIES OF THE SERIES

Case No.	Age of Mother (years)	Parity	Sex of Infant	Birth Weight of Infant (lb. oz.)	Protein-bound Level in Mother (μg./100 ml.)	Protein-bound Level in Infant (μg./100 ml.)
1	24	Primigravida + 1 miscarriage	M.	6 0¼	7·2	4·3
2	22	Primigravida	F.	6 12¾	6·2	3·8
3	20	Primigravida	F.	7 13	12·2	9·0
4	27	Primigravida + 1 miscarriage	M.	6 9	4·9	2·3
5	39	7	M.	7 13½	5·7	4·9
6	26	Primigravida	M.	7 10½	7·0	9·0
7	24	3	M.	9 8	8·0	10·3
8	22	Primigravida	M.	6 5½	9·1	11·6
9	18	Primigravida	F.	7 2	11·6	4·5
10	24	1	M.	7 15	3·0	3·5
11	28	3	M.	9 12½	9·5	8·2
12	24	Primigravida	F.	6 12½	10·3	9·6
13	25	2	M.	6 1	7·8	6·7
14	39	5 + 2 miscarriages	M.	8 15	11·0	8·5
15	33	2 + 3 miscarriages	F.	7 0	4·1	3·5
16	37	8	F.	9 13½	8·3	4·0
17	18	Primigravida	M.	7 9¾	7·0	5·1
18	25	Primigravida + 1 miscarriage	M.	6 15¾	9·4	9·2
19	35	Primigravida	M.	5 15¾	6·2	4·9
20	34	7	F.	6 11½	3·8	3·2
21	26	Primigravida	M.	5 13¾	12·4	4·4
22	22	Primigravida	M.	6 7	12·0	4·0
23	18	Primigravida	M.	8 0¾	7·5	7·9
24	27	Primigravida	M.	6 9	7·5	5·6
25	20	Primigravida	M.	8 15½	5·7	4·4
26	32	1	M.	8 1½	7·8	7·3
27	25	1	M.	7 4	5·3	3·7
28	26	Primigravida	M.	8 6½	10·7	4·2
29	32	Para 2 + 1 ectopic	M.	6 12¾	5·7	6·6
30	19	Primigravida	F.	7 10	4·1	3·6
31	33	4	F.	7 14	5·0	4·7
32	29	3	F.	7 8½	3·8	2·4
33	27	Primigravida	F.	7 2½	5·6	2·0

details of the age and parity of the mothers and the sex and birth weights of the infants.

Discussion

Thirty-three cases were included in this study. In six cases the protein-bound iodine level was higher in the infant's cord blood than in the mother's blood; these cases were all males. The protein-bound iodine levels in the mother's blood ranged from 3·0 to 12·4 μg. per 100 ml. and in the infant's cord blood from 2·0 to 11·6 μg. In 21 of the mothers and also in 21 infants the protein-bound iodine level range was between 3·5 and 8 μg. per 100 ml. and in only one mother and four infants was the level below 3·5 μg. per 100 ml. In 11 mothers and eight infants the level was over 8·0 μg. per 100 ml.

Summary

Protein-bound iodine levels in the blood of mothers and their newborn infants were studied with a view to establishing a normal pattern.

We wish to thank the Director of the Institute for his interest, Prof. C. S. Heyns, Dr. L. G. R. van Dongen and Dr. F. Daubenton for allowing us the facilities at the Queen Victoria Maternity Hospital, the labour ward staff for their kind cooperation and Mrs. J. K. Purchase for her technical assistance.

References

Connor, A. C., Swenson, R. E., Park, C. W., Gangloff, E. C., Lieberman, R. and Curtis, G. M. (1949). *Surgery*, 25, 510.
Kennedy, R. L. J. and Hayles, A. B. (1948). Brennemann's *Practice of Pediatrics*, vol. 1, Chapter 38, p. 6. Hagerstown, Maryland.
Van Zyl, A. (1953). *S. Afr. J. med. Sci.*, **18**, 61.
Wright, Samson (1952). *Applied Physiology*, 9th ed., p. 976. London.

PHENYLKETONURIA WITH NORMAL INTELLIGENCE AND GOWERS' MUSCULAR DYSTROPHY

BY

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Phenylketonuria is a rare inborn error of metabolism, which is believed to be associated almost always with some degree of mental retardation. The great majority of those affected are idiots or imbeciles; any with an intelligence quotient over 65 are rare enough to merit reporting (*e.g.*, Low, Armstrong and Carlisle, 1956). Gowers' peripheral muscular dystrophy is also a very unusual disease in children. The case reported here showed this extremely rare combination of Gowers' muscular dystrophy, phenylketonuria and an intelligence quotient of over 100. It appeared important, therefore, to determine any metabolic or other differences between this case and other phenylketonurics in the hope of throwing more light on the disease process.

Case History

A.T. was the fourth child of a family of five, born on July 29, 1948, a full-term male infant, weighing 6 lb. 3 oz. His progress was normal at first, and he used his hands well as a baby, but did not walk until the age of 20 months. He played normally with toys.

In June, 1951, when he was almost 3 years old, his mother noticed that he was holding the right hand as if there were no power in that wrist. She then noticed that he could no longer hold a knife in the right hand nor open a door with it.

In January, 1952, he was found to have bilateral wrist drop, with hyperextension of the metacarpo-phalangeal joints. There was no obvious weakness elsewhere.

From the age of 3½ years to 5 years there was no great change in his condition, although he possibly became a little more clumsy, but during his fifth year his mother noticed that he seemed to slap his feet down when walking. He began to tire easily and had to be taken about in a wheeled chair. He also began to have attacks of abdominal distension and vomiting, lasting about 24 hours.

He was referred to The Hospital for Sick Children in the autumn of 1954 by Dr. I. H. Gosset. It was then noted that his face was somewhat expressionless and that he had a tendency to allow his mouth to gape open. He had a left internal squint. There was bilateral wrist drop with a flexion deformity of the fingers. There was wasting of the small muscles of both hands and the right forearm, bilateral pes cavus, and weakness of dorsiflexion of both feet with a tight Achilles tendon on both sides. The right deltoid and sternomastoid muscles as well as the right arm muscles were found to be weak. There were no sensory changes.

A diagnosis of muscular dystrophy of Gowers' type was made.

Electromyogram. Dr. A. T. Richardson reported as follows: The electromyogram showed normal intensity-duration curves of the right tibialis anterior. There was no spontaneous activity and on volition there was a full interference pattern of short-duration and polyphasic motor unit potentials with a significant increase in high frequency component.

These findings are typical of a myopathic lesion. There was no evidence of denervation or of degeneration of the lower motor neurones.

Biopsy. Dr. Martin Bodian reported that a biopsy specimen of muscle showed considerable variation in the size of the individual muscle fibres; large and small fibres were scattered haphazardly throughout the muscle bundles. The large fibres sometimes showed degenerative changes and in a considerable number of them the cross striations were difficult to make out, because of homogenization and hyalinization of the sarcoplasm. Occasionally the fibres were definitely split. Degenerative changes were also seen in many of the small fibres. The sarcolemmal nuclei were enlarged and more pleomorphic than usual, but they did not appear to occupy a central position on the fibres (which is said to be a special feature of myotonic dystrophy). There was an increase of the interstitial fatty tissues and fatty replacement of some of the degenerate muscle fibres. The interstitial tissues contained numerous arterioles and venules and all the former were thick-walled and often showed hyaline changes in their walls. There was no inflammatory cell infiltration. Special techniques revealed that nerve fibres and motor end-plates were present, and that they showed no histological abnormalities. The appearances were those of a muscle dystrophy.

Radiograph of Cervical Spine. No abnormality was seen beyond rather large rib elements to the seventh cervical vertebra.

Chemical Investigations

At the time this case was seen, we were looking for amino-aciduria in muscular dystrophy and in consequence the urine of this case was examined by paper chromatography.

The cerebrospinal fluid, blood and urine gave paper chromatogram patterns characteristic of phenylketonuria, with a very large excess of phenylalanine over the normal and with all other amino-acids normal. The concentration of phenylalanine in the cerebrospinal fluid was 30 μg. per ml., that in the fasting blood serum was 50 μg. per ml., and in the post-prandial blood serum 180 μg. per ml. These values were estimated from the paper chromatograms and the accuracy of these figures is only ±25%.

Several 24-hour specimens of urine were examined; the results are given in Table 1. Phenylpyruvic acid was estimated by the method of Berry and Woolf (1952), phenylalanine, phenyllactic acid and phenylacetylglutamine by modifications (Woolf, in preparation) of the Kapeller-Adler (1934) method and the phenolic acids by a modified Millon's reaction (Berry and Woolf, 1952; Woolf, in preparation).

TABLE 1.
EXCRETION WHILE ON A NORMAL DIET
(FIVE SPECIMENS)

Substance	Range (mg. per 24 hours)
Phenylpyruvic acid	142–207
Phenyllactic acid	98–168
Phenylalanine	128–160
Phenylacetylglutamine	385–690
Phenolic acids (* total)	97–117
Phenolic keto-acids*	65– 90

* As tyrosine.

An ethereal extract of the urine gave on paper chromatography and development with Ehrlich's reagent two purple spots with the R values of indolyllactic and indolylacetic acid respectively. Similar spots were given by urine from other phenylketonurics but not from normals (*cf.*, Armstrong and Robinson, 1954); the concentrations of the abnormal indole derivatives in this child's urine were a little above the average though within the range found for phenylketonurics.

Every specimen of urine examined while the child was on a normal diet gave an unmistakable green colour with ferric chloride, but the intensity was less than that usually seen.

On treatment with a diet low in phenylalanine, just as in other phenylketonurics, phenylpyruvic acid, phenyllactic acid and abnormal indole and phenolic compounds vanished from the urine, while the concentrations of phenylalanine in the blood and urine dropped to normal, as did his excretion of phenylacetylglutamine.

The urine of the patient's father, mother, sister and three brothers showed no excess of phenylalanine on paper chromatograms.

The child's hair was medium brown. The percentage reflection of light at various wavelengths is given in Table 2. There was no appreciable further darkening during the three months that the child was fed on a diet low in phenylalanine (*cf.*, Cowie and Penrose, 1951; Woolf, Griffiths and Moncrieff, 1955).

TABLE 2.
HAIR COLOUR

Wavelength (mμ.) ..	700	670	600	580	550	520	490	470	430
Reflectance (%) ..	9	8	6	4·5	4·5	4·5	4	4	3·5

Psychological Investigations

The tests demonstrated that A.T. was of average intelligence. This was true whether verbal or non-verbal tests were used. The slightly lower Wechsler scale measures were the result of the comparative failure in 'object assembly' where the muscular dystrophy had most effect; in any case a measure calculated from only three sub-tests cannot be as reliable as the Binet scale result.

TABLE 3.
INTELLIGENCE TEST RESULTS IN A.T.

Date	Chronological Age	Mental Age	I.Q.
Revised Stanford Binet Form L.			
3.12.54	6 yr. 4 mth.	6 yr. 6 mth.	103
28. 1.55	6 yr. 5 mth.	6 yr. 6 mth.	101
29. 4.55	6 yr. 8 mth.	7 yr. 0 mth.	105

Date	Picture Completion (%)	Picture Arrangement (%)	Object Assembly (%)	Performance Scale I.Q.
Wechsler Intelligence Scale for Children				
9 12.54	50	45	30	87
29. 4.55	65	40	30	93

Date	Set A	Set A_B	Set B	Score	Grade	Percentile Rank
Progressive Matrices (1947)						
3.12.54	7	4	5	16	III+	50
29. 4.55	10	2	2	14	III−	26

Date	First Trial (sec.)	Second Trial (sec.)	Third Trial (sec.)
Seguin Form Board			
23.1.55	65	51	53
29.4.55	45	37	28

Retesting was carried out (Table 3) to measure the effect of three months on a phenylalanine-restricted diet. There were no significant differences in intelligence test measure. On retesting, the matrices test was given last of four tests, and A.T. was clearly very tired, and gave an inconsistent score pattern; this result is not reliable and does not invalidate the earlier result.

The Seguin form board was given to measure manual dexterity, the muscular dystrophy making it, of course, valueless as a test of intelligence. The time was almost halved after three months of dietary treatment, which may be significant. It may, however, reflect the results of practice in using his hands.

A.T.'s eldest brother obtained a grammar school scholarship. It, therefore, seemed possible that A.T.'s score might be below the family average. All the family except the baby sister were therefore tested (Table 4).

TABLE 4.
RESULTS OF INTELLIGENCE TESTS ON A.T's FAMILY

	Chronological Age	Verbal I.Q.	Performance I.Q.	Full Scale I.Q.
Wechsler Bellevue Scale Form L				
Father ..	34 yr.	104	112	109
Mother..	35 yr.	126	119	125

Sib	Chronological Age	Mental Age	I.Q.
Revised Stanford Binet Form L			
G.T.	11 yr. 6 mth.	16 yr. 9 mth.	142
P.T.	9 yr. 11 mth.	10 yr. 6 mth.	106
R.T.	7 yr. 9 mth.	8 yr. 10 mth.	114

The father's performance scale I.Q. of 112, equivalent to a Binet I.Q. of 117, is probably more reliable, from objective evidence, than the verbal measure of 104. P.T.'s score is probably an underestimate; he was a disturbed boy who after a great deal of ill health was attending an open-air school; the supposition that this may have reduced the measure is supported objectively by the score pattern. His innate I.Q. was probably 116. A.T., therefore, measured about 10 I.Q. points below the next lowest member of his family, or 18 I.Q. points below the family average in Binet terms.

Discussion

This is the only known untreated case of phenylketonuria with an intelligence rating of over 100. Only one other case has been reported with an I.Q. close to this figure (average score of 94 on four intelligence tests, Cowie, 1951). A handful of cases have intelligence quotients ranging from 60 to 90, but in the majority the I.Q. is less than 30.

The distribution of intelligence among phenylketonurics is shown in Fig. 1 (Penrose, 1951). The mean intelligence quotient is 23 and the standard deviation ± 14, but the curve is very markedly skewed. Moreover, the data are drawn almost exclusively from patients in institutions and their relatives, which must result in the exclusion of some of the higher grade phenylketonurics. That the number so excluded is not very large is shown by the finding by Vulliamy and Woolf (unpublished) of only one case during a search for high-grade phenylketonurics among 2,200 educationally subnormal children of I.Q. 50 to 70 (*cf.*, Larson, 1956). In these circumstances it is difficult to do more than guess at the proportion of phenylketonurics with intelligence in the normal range, but it seems unlikely to be higher than 0·1%.

The theory that the mental deficiency in phenylketonurics is due to an intoxication by phenylalanine or one of its abnormal metabolites (Woolf and Vulliamy, 1951) has been confirmed by the success of a low-phenylalanine diet in preventing or partially reversing the mental deficiency (Woolf *et al.*, 1955; Bickel, Gerrard and Hickmans, 1953; Armstrong and Tyler, 1955; Braude, 1956; Horner and Streamer, 1956).

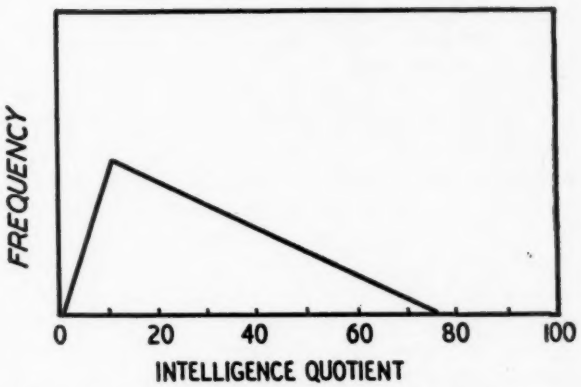

FIG. 1.—Diagram illustrating the distribution of intelligence quotient among phenylketonurics (from Penrose, 1951).

In the case reported here (as shown above) the patient's test scores are rather lower than might have been expected from the family results, and it is possible that some mental deterioration has occurred. The deterioration is, however, minimal, and quite negligible compared with that undergone by most phenylketonurics.

The chemical investigations revealed no qualitative differences between this patient and other phenylketonurics. The phenylalanine concentration in the C.S.F. was high, as in other phenylketonurics, indicating no difference in permeability of the blood-brain barrier that might account for the lesser mental damage. The phenylalanine concentration in post-prandial blood and the urinary excretion of phenylalanine were not markedly different from those found in other phenylketonurics of this age-group. The urinary excretion of phenylacetylglutamine was variable but within the range found for other phenylketonurics. Indolyllactic and indolyl-

acetic acids were present in the urine in concentrations which were no lower than those found in other phenylketonurics (Armstrong and Robinson, 1954), and very much higher than in normal individuals; this was also true of the ketonic and non-ketonic phenolic acids (Berry and Woolf, 1952).

The daily excretion of phenylpyruvic acid was only about one-quarter to one-seventh of that found in other phenylketonurics, and the excretion of phenyllactic acid was also rather lower. It is noteworthy that another case of phenylketonuria with high intelligence also excreted less than the average amount of phenylpyruvic acid (Cowie, 1951), while Følling (private communication, cf. Følling, Mohr and Ruud, 1945) found a low and intermittent excretion of this acid in some phenylketonurics who were intelligent enough to attend ordinary schools though not to do well there.

The medium brown hair colour in this patient, and the almost black hair in the case described by Cowie (1951), contrast sharply with the grey-blond hair so often found in phenylketonurics. Dancis and Balis (1955) ascribed this pale hair to an inhibition of melanin formation by a high concentration of phenylalanine, but other factors may also be active *in vivo*. The correlation of normal hair colour with normal intelligence in these two cases can hardly be coincidence; it suggests either a lower concentration of some inhibiting substance or a greater resistance to inhibition of the chemical reactions needed for melanin formation and for the transmission of neural impulses.

The idea is inescapable that there is some connexion between the higher intelligence and the lower excretion of phenyllactic acid and phenylpyruvic acid. Low *et al.* (1956) suggest that in some high-grade cases of phenylketonuria the metabolic block is only partial and some phenylalanine is converted to tyrosine. This becomes more acceptable if one adopts Pauling's (1955) idea of a 'molecular disease' as applied to phenylketonuria by Knox (1956). According to this view, the mutant gene for phenylketonuria is incapable of carrying out an essential stage in the synthesis of the enzyme phenylalanine hydroxylase, and some other protein, which is enzymatically inactive, is produced instead. Phenylketonuria results when an individual is homozygous for this mutant gene. It is, however, possible that another allele at the same locus synthesizes a protein with appreciable, though greatly reduced, enzyme activity. If this were the case it could account for the biochemical results found in some high-grade phenylketonurics.

An alternative possibility is that the renal tubular reabsorption of phenylalanine is, for some reason, relatively inefficient in certain cases. This would result in a lowering of the concentrations of phenylalanine and its abnormal metabolites in the blood and tissues, and so reduce the degree of intoxication. The low concentration of phenylalanine in the blood of A.T. after an overnight fast lends some support to this hypothesis. Følling *et al.* (1944) found that phenylpyruvic acid was absent from some early morning specimens of urine from an educable phenylketonuric; this would also fit in with the above hypothesis since phenylpyruvic acid is not excreted when the blood phenylalanine concentration falls below a certain level. A low kidney threshold for phenylalanine would have to operate from earliest infancy if it were materially to reduce the degree of mental deficiency. It should be possible to test these alternative hypotheses using recently devised techniques.

The non-specific hydroxylation mechanism (Dalgliesh, 1954, 1955; Brodie, Axelrod, Shore and Udenfriend, 1954; Udenfriend, Clark, Axelrod and Brodie, 1954; Udenfriend and Bessman, 1953) cannot account for the low excretion of phenylpyruvic and phenyllactic acids in this case. Both *ortho-* and *para*-hydroxy derivatives are produced in equivalent amounts by this mechanism and the former are excreted. The excretion of such phenolic compounds in this case was no higher than that found in other phenylketonurics.

Treatment for three months with a diet low in phenylalanine did not cause any clinically detectable improvement in the muscular dystrophy. There was no significant increase in intelligence, though this was not unexpected after so short a course of treatment. It did not seem justifiable to prolong treatment with an artificial diet in a child of this age and mental development. The absence of any further darkening of the hair while on this diet supports the suggestion that melanin formation was not interfered with in this patient.

No connexion can be traced between muscular dystrophy and phenylketonuria. Other phenylketonurics show no clinical evidence of muscular dystrophy and their electromyograms are normal (Richardson, private communication). It is improbable that a tendency towards muscular dystrophy on the part of phenylketonurics should become overt in the one case whose mentality is hardly affected. Ten other cases of muscular dystrophy have been examined and found to excrete no phenylpyruvic acid or excess of phenylalanine (Woolf, unpublished). Moreover, there are no reports in the literature of muscular dystrophy associated with phenylketonuria. We conclude that this is a chance combination of the two conditions.

Summary

A case of phenylketonuria with an intelligence quotient of 103 and with peripheral muscular dystrophy is described. The patient excreted less phenylpyruvic and phenyllactic acids than most phenylketonurics. The correlation of mentality and biochemistry is discussed.

Addendum

This child was seen again in May, 1957. The serum 5-hydroxytryptamine was estimated by Dr. Stacey, and found to be 165 m.μg. per ml., which is well within the normal range, and far more than that found in most phenylketonurics (Pare, Sandler and Stacey, 1957).

His intelligence quotient was determined again, using the same battery of tests as before, and it was found to have fallen as follows: Revised Stanford-Binet I.Q., 89; progressive matrices, 1947, percentile rank: 10; Wechsler intelligence scale for children, performance I.Q., 83. The consistent direction of these changes makes them more probably significant. Thus, over a period of two years and one month the child's I.Q had fallen by an average of 18 points, suggesting deterioration. In view of this and his mother's feeling that he had been better while on a low phenylalanine diet, this diet has once more been instituted.

We are grateful to Dr. A. T. Richardson for the electromyographic reports on A.T. and on other phenylketonurics, and to Dr. Martin Bodian for examining the muscle biopsy specimen. We are grateful also to Mrs. V. Cowie who determined the hair reflectance at different wavelengths and to Dr. I. H. Gossett for obtaining specimens of urine from the patient's family. We wish to thank the patient's family for submitting to intelligence tests, the Northampton Education Authority for their cooperation, the dietitian and nursing staff at Great Ormond Street and Tadworth Court for feeding the special diet and collecting specimens. Professor L. S. Penrose kindly permitted us to use Fig. 1. The Research Committee of The Hospital for Sick Children awarded one of us (L.I.W.) a research fellowship and financed the investigation.

References

Armstrong, M. D. and Robinson, K. S. (1954). *Arch. Biochem. Biophys.*, **52**, 287.
—— and Tyler, F. H. (1955). *J. clin. Invest.*, **34**, 565.
Berry, J. P. and Woolf, L. I. (1952). *Nature (Lond.)*, **169**, 202.
Bickel, H., Gerrard, J. and Hickmans, E. M. (1953). *Lancet*, **2**, 812.
Braude, H. (1956). *S. Afr. med. J.*, **30**, 83.
Brodie, B. B., Axelrod, J., Shore, P. A. and Udenfriend, S. (1954). *J. biol. Chem.*, **208**, 741.
Cowie, V. A. (1951). *Lancet*, **1**, 272.
—— and Penrose, L. S. (1951). *Ann. Eugen. (Camb.)*, **15**, 297.
Dalgliesh, C. E. (1954). *Biochem. J.*, **58**, Proc. p. xlv.
—— (1955). *Arch. Biochem. Biophys.*, **58**, 214.
Dancis, J. and Balis, M. E. (1955). *Pediatrics*, **15**, 63.
Følling, A., Mohr, O. L. and Ruud, L. (1955). *Skr. norske Vidensk.-Akad.*, I. *Mat.-nat. Kl.* 1944, No. 13.
Horner, F. A. and Streamer, C. W. (1956). *J. Amer. med. Ass.*, **161**, 1628.
Kapeller-Adler, R. (1934). *Biochem. Z.*, **271**, 206.
Knox, W. E. (1956). *Bull. Tufts-New Engl. med. Cent.*, **2**, 1.
Larson, C. A. (1956). In Gedda *Novant' anni delle Leggi Mendeliane*, p. 311. Rome.
Low, N. L., Armstrong, M. D. and Carlisle, J. W. (1956). *Lancet*, **2**, 917.
Pare, C. M. B., Sandler, M. and Stacey, R. S. (1957). *Lancet*, **1**, 551.
Pauling, L. (1955). *Harvey Lect.* (1953-1954), **49**, 216.
Penrose, L. S. (1951). *Ann. Eugen. (Camb.)*, **16**, 134.
Udenfriend, S. and Bessman, S. P. (1953). *J. biol. Chem.*, **203**, 961.
——, Clark, C. T., Axelrod, J. and Brodie, B. B. (1954). *Ibid.*, **208**, 734.
Woolf, L. I. and Vulliamy, D. G. (1951). *Archives of Disease in Childhood*, **26**, 487.
——, Griffiths, R. and Moncrieff, A. (1955). *Brit. med. J.*, **1**, 57.

PERIPHERAL VASOMOTOR FUNCTION IN CRETINISM

BY

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'Diminution or stasis of the peripheral circulation are usually manifested by striking changes in the appearance of the skin and mucous membranes. The skin is pale and cool and often has a grayish mottled appearance. . . . A warm, moist skin and a high, ruddy colour are strong evidences against thyroid deficiency.'

These features of poor peripheral circulation which Lawson Wilkins (1950) emphasizes in his description of hypothyroidism in childhood are well-known physical signs and, as he says, are often of diagnostic value. They are usually included in a description of the bradycardia, hypotension and other signs of a slowly functioning cardiovascular system in textbook descriptions of the disease, and it is thereby implied that the skin is cold and cyanosed because of poor cardiac output. Yet another explanation is possible. They might be due to absence or inadequacy of the vasodilatation reflex, so that warm stimuli on any part of the body surface, which would normally initiate general vasodilatation in the skin, fail to do so. Indeed, a depression of vasomotor reflexes might be expected in a disease where all functions, in particular other reflexes and evidences of nervous activity, are depressed. However, no experimental study of vasomotor reflexes in hypothyroidism has been found in the literature. Talbot (1931) studied the resting skin temperatures of 10 untreated cases, 22 treated cases and 27 normals, and confirmed the lower skin temperature in the cretins. The difference was particularly marked at the extremities. He then exposed them nude to room temperature and found that the average fall at the extremities was less than occurred in normals. There are several possible explanations for this result, but at least it can be concluded that there was no evidence of an exaggerated vasoconstrictor response to cold, which would be one possible explanation of poor peripheral circulation.

The present investigation was undertaken to find out whether reflex vasodilatation is impaired in cretinism. Five cases of previously untreated cretinism and one case of treated cretinism were investigated before and at intervals during treatment.

Method of Investigation

A modification of the limb-immersion method of Gibbon and Landis (1932) was used for those infants and young children unable to cooperate. Details of technique will be found elsewhere (Bower, 1954, 1956). Briefly the method is as follows:

The infant is undressed and secured on a canvas sheet on his right side, his arm passing through a hole in the canvas into a heat-lagged can containing water at 42 to 44° C. Thermocouples measure the temperature of the feet and unimmersed hand at intervals before and during arm immersion, which is continued until either the temperature of the unimmersed extremities has reached a maximum or it is clear that the response is absent or grossly delayed. Hand temperature is taken from the skin on the dorsum of the hand just proximal to the metacarpophalangeal joints between the second and third metacarpals, and foot temperature from a corresponding point on the foot between the first and second metatarsals. Thermocouples are also used throughout the experiment to measure the temperature of the air above the cot and the water in the can and the temperature of the latter is maintained at 42 to 44° C. by frequent partial replacement of the cooling water with hot water.

Those children old enough to cooperate sit on a chair with the right arm in a basin of water at 42 to 44° C. Temperatures are recorded in the same way as in the infants.

Three values are then obtained from the time-temperature graph of each limb (Fig. 1):

T_R = the time interval between arm immersion and the start of reflex temperature rise (minutes)

T_{max} = the time interval between arm immersion and the attainment of a maximum temperature (minutes)

m.t. = the maximum temperature attained (°C.)

It is theoretically desirable to perform each experiment at the same environmental temperature and to start heating the limb only when the skin temperatures of the unimmersed extremities are at standard levels. However, in practice it has been found that under the condi-

tions of these experiments room temperature and initial limb temperatures are unimportant factors in determining the nature of the response by comparison with the heating stimulus applied to the immersed limb.

The Normal Response in Infancy and Childhood

Reflex vasodilatation occurs as rapidly and completely in the normal child and in the normal infant over approximately 3 months of age as in the adult (Bower, 1954, 1956). With the method of investigation described, this adult type of response fulfils the following criteria: T_R(feet) is less than 15 minutes, T_{max} (feet) is less than 40 minutes, m.t. (feet) is greater than 34° C., where each of these values is the mean of the values for the two feet. (It has been found that the behaviour of the feet in this respect is more consistent than that of the hands, and it is the former which is emphasized in the present study. A typical result is shown in Fig. 1.)

The Response in Cretinism: Material and Results

Case 1. A.R., a girl, was aged 4½ months at the time of the first test.

First child. Born by caesarean section at term. Birth weight 10 lb. 11¼ oz. Had always been difficult to feed and at 4½ months still took an hour for each feed. A placid baby. Had been constipated only recently. An umbilical hernia had been present from birth and was increasing in size.

TABLE 1
RESULTS OF REFLEX VASODILATATION TESTS IN THE FEET

Case	Weeks after Start of Treatment	Response in the Feet (mean values for the two feet)		
		T_R (minutes)	T_{max} (minutes)	m.t. (°C.)
A.R. ..	0	No rise over 52 minutes		
	2	34	56	29·2
	3	33	56+	22·2+
	4	27	54+	34·3+
	11	2	45	33·4
B.M. ..	0	No rise over 55 minutes		
	3	12	55+	33·8+
	8	<4	30	35·5
G.E. ..	0	24	60	33·2
	3	6	33	35·6
S.G. ..	0	6	29	32·9
	4	<1	26	34·2
C.C. ..	0	No rise over 48 minutes		
	3½	3	22	35·4
P.T. ..	0	8	28	35·2

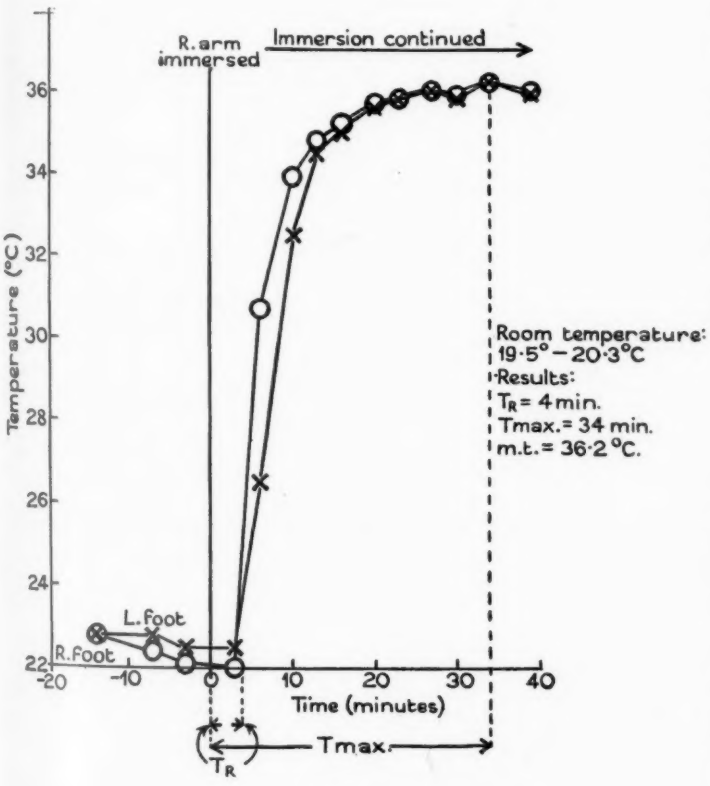

FIG. 1.

EXAMINATION. A typical cretin with a placid expression, coarse features, a dry, yellow, cold skin, protruding tongue, supraclavicular pads of fat, a hoarse monotonous cry, and a very large umbilical hernia. Weight 13 lb. 2 oz. Rectal temperature subnormal.

INVESTIGATIONS. Haemoglobin 78%, bone age subnormal, serum cholesterol level 226 mg. per 100 ml. and an electrocardiogram showed T waves flat in all leads consistent with mild hypothyroidism.

PROGRESS AND TREATMENT. Treatment was started on the day of the first test and was continued in the following dosage scheme:

1st to 10th day	..	grain ¼ daily
10th to 16th day	..	grain ½ daily
16th to 23rd day	..	grain ¾ daily
23rd to 36th day	..	grain 1 daily
36th day onwards	..	grain 1½ daily

Her response was slower than expected and she eventually required more thyroid than does the average cretin at this age.

REFLEX VASODILATATION TEST (Table 1). Tests were done at intervals after treatment.

First Test. There was no definite evidence of vasodilatation in any limb over 52 minutes (Fig. 2). There were slight temperature rises in the hand and left foot but these indicate an insignificant degree of vasodilatation in this temperature range. The rectal temperature was also recorded, and it is interesting that it rose 0·5° C.

during the first 20 minutes. This is evidence of a stimulus which would be quite sufficient to produce a response in the normal.

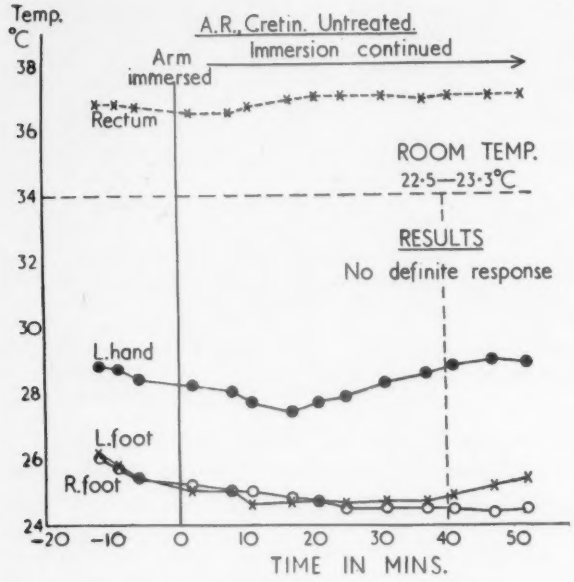

FIG. 2.

Second Test after 14 Days' Treatment. (At this time she had shown a slight but definite response to treatment.) There was a definite but delayed and subnormal response in all three limbs (Fig. 3).

Third and Fourth Tests after 24 and 29 Days' Treatment. The third test gave a response almost identical with that in the second. The fourth test still showed delay but the final temperatures were all over 34° C.

Fifth Test after 11 Weeks' Treatment. (At this time she was normal in appearance and behaviour.) An adult response (Fig. 4): although T_{max} and m.t. are slightly outside adult limits this can be accounted for by the fact that she had just come in from the street on a cold day and consequently the initial limb temperatures were unusually low. (The previous tests had been performed as an in-patient.)

SUMMARY. A typical cretin at 4½ months, her extremities showed no definite response to limb heating over 52 minutes. There was a partial response after two weeks' treatment when she had shown only a slight clinical improvement. There was slight progress towards normality in the limb responses over the next two weeks. After 11 weeks, when she was clinically euthyroid, her temperature curves were of the adult type.

Case 2. B.M., a boy, was aged 6 months at the time of the first test.

First child. Birth weight 9¼ lb. Normal delivery. Had caused no anxiety until he was 4 months old, when his mother realized that he was slow in feeding and was not gaining weight well. Constipated and very lethargic. These symptoms continued until he was brought to hospital at 6 months.

EXAMINATION. A typical cretin with coarse features, dry, yellowish skin, sparse hair, supraclavicular pads of fat, an umbilical hernia, bradycardia, hypothermia and a croaking, monotonous cry. He had a prolonged reaction time to stimuli. His hands and feet were cold and cyanotic.

INVESTIGATIONS. Haemoglobin 72%.

PROGRESS AND TREATMENT. Thyroid, grain $\frac{1}{8}$ daily, was given orally from the day of the first test. After seven days the dose was increased to grain $\frac{1}{4}$ daily. After three weeks' treatment, at the time of the second test, he had become more lively, was crying more, had lost 1 lb. in weight, and his constipation had improved. His appearance was relatively unaltered but his skin was

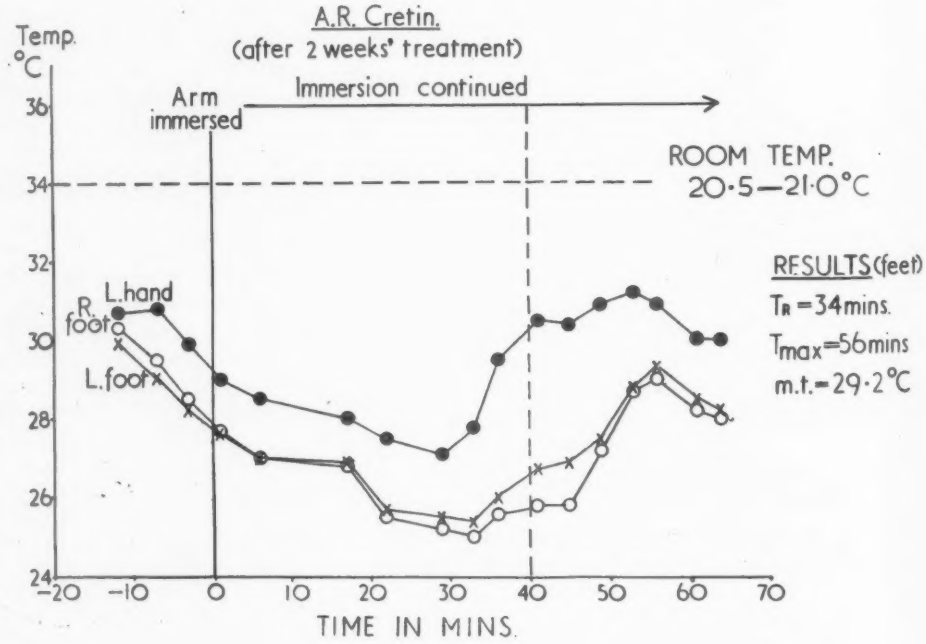

FIG. 3.

loose and hanging in folds. At the time of the third test, after eight weeks' treatment, he was normal in behaviour, active, smiling and chuckling, and almost normal in appearance, the skin texture and colour being much improved and the scalp being covered with new hair.

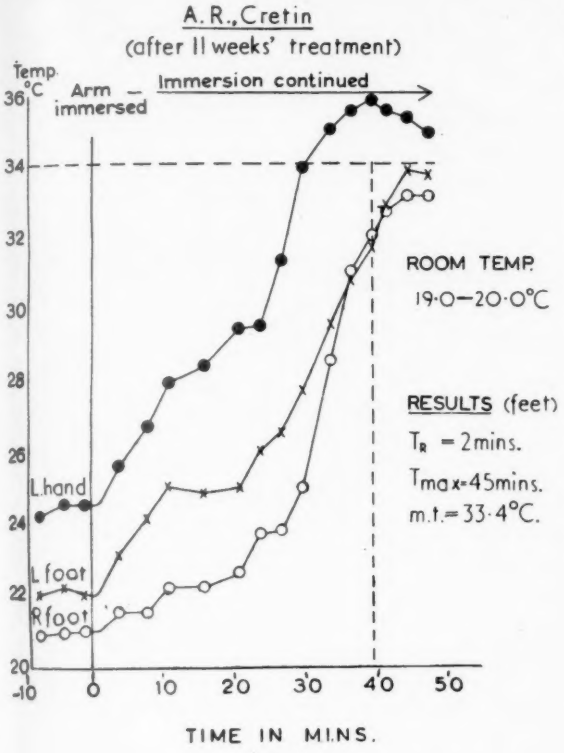

FIG. 4.

REFLEX VASODILATATION TESTS. The results are shown in Table 1.

First Test. There was no response in any limb over 45 minutes. By the time the test was terminated (55 minutes) the temperature of the hand not immersed had started to rise but there was still no response in the feet.

Second Test after Three Weeks' Treatment. A response in all three limbs but still outside normal limits for the age.

Third Test after Eight Weeks' Treatment. The response was normal in all three limbs.

SUMMARY. A typical cretin at 6 months, his extremities showed no response to a heating stimulus over 45 minutes. After three weeks' treatment, when he was just starting to respond clinically, he showed a definite but sluggish response to limb heating. After eight weeks, when he appeared euthyroid, he showed an adult type of response.

Case 3. G.E. was 2½ years at the time of the first test. Fifth child. Normal birth and neonatal history. Had always been slow in movements. Retarded motor development (not walking or talking at 2½ years, and had been standing only for a few months). Skin had always been cold and dry. Always constipated.

EXAMINATION. A typical cretin with coarse features, protruding tongue, pale dry skin, cold and cyanotic extremities, a croaking voice, short neck with supraclavicular pads, and a large abdomen with an umbilical hernia. Under height by 8½ in. Slightly under weight. Temperature subnormal.

INVESTIGATIONS. Haemoglobin 62%, bone age under 6 months, serum cholesterol level 338 mg. per 100 ml.

PROGRESS AND TREATMENT. Treatment was started on the day of the first test and was continued on the following dosage scheme:

1st to 10th day	..	grain ⅛ daily
10th to 22nd day	..	grain ¼ daily
22nd day onwards	..	grain ½ daily

She was more alert and responsive at the time of her second test, after three weeks' treatment. Her skin was warmer and more normal in appearance, and she had lost 1 lb. in weight.

REFLEX VASODILATATION TESTS. The results are shown in Table 1.

First Test. There was a delayed response in all limbs with low maxima.

Second Test after Three Weeks' Treatment. There was a brisk response with higher maxima—an adult type of response.

SUMMARY. A typical cretin at 2½ years, she showed a delayed response in all limbs and reached subnormal maxima. After three weeks' treatment the response was normal.

Case 4. S.G., a girl, was aged 2 years 11 months at the time of the first test.

Full term. Normal delivery. Birth weight 8 lb. Neonatal period normal. From the age of 3 months feeding had been difficult and during the second year her appetite was extremely poor. Sat up at 12 months, walked at 2 years. First spoke words at 2 years. Teeth first appeared at 10 months. Often was cold to the touch. A fairly active child. Bowel action every other day.

EXAMINATION. An irritable, active child. Under height (6 in.). Under weight (6 lb.). Appearance not obviously cretinous. Features moderately coarse. Open fontanelle. Fine hair. Waddling gait. Skin dry but not cold, with a yellowish tinge. Temperature subnormal. Some thyroid tissue probably present.

INVESTIGATIONS. Haemoglobin 81%, bone age below 3 months, serum cholesterol level 320 mg. per 100 ml.

PROGRESS AND TREATMENT. Treatment was started on the day of the first test and was continued on the following dosage scheme:

1st to 7th day	..	grain ⅛ daily
7th to 14th day	..	grain ¼ daily
14th day onwards	..	grain ½ daily

She made slight but definite progress on treatment and at the time of the second test, after four weeks' treatment, she was livelier, looked more normal, and had shed some hair.

REFLEX VASODILATATION TESTS. The results are shown in Table 1.

First Test. An adult response as regards timing but maximum temperatures slightly subnormal.

Second Test after Four Weeks' Treatment. An adult response. The initial temperatures were higher than on

the previous occasion (room temperatures on the two occasions only differing by 1·0-1·5° C.) and the maximum temperatures were above 34° C.

SUMMARY. A mild but definite cretin, she responded normally as regards timing but did not attain the usual adult maxima in the feet. After treatment the extremities were much warmer before arm immersion at a comparable room temperature, and she attained normal adult maxima.

Case 5. C.C., a girl, was aged 3½ years at the time of the first test.

First child. Full term. Forceps delivery. Birth weight 6 lb. 11 oz. Had always been a good, quiet child. Late in acquisition of motor facilities (sat up at 12 months, walked at 2½ years, first spoke at 12 months but had added only a few words to her vocabulary since then). Slow and unsteady on her feet. Hands and feet blue and cold. Always constipated. Only possessed two teeth at 2 years.

Had been treated with thyroid six months before but only for one month.

EXAMINATION. A moderately severe cretin, although the diagnosis was not immediately obvious. Under height (5½ in.). Under weight (4 lb.). Skin dry and cool. Complexion pale ('strawberries and cream'). Hair sparse. Fontanelle open. Slow in all her movements. Temperature subnormal.

INVESTIGATIONS. Haemoglobin 74%, bone age, marked immaturity, serum cholesterol level 610 mg. per 100 ml.

PROGRESS AND TREATMENT. Treatment was started on the day of the first test and was continued on the following dosage scheme:

1st to 12th day .. grain ¼ daily
12th day onwards .. grain ⅜ daily

She made a definite response to treatment and after three and a half weeks, at the time of the second test, was more lively and less constipated.

REFLEX VASODILATATION TESTS. The results are set out in Table 1.

First Test. There was no response in the feet over 48 minutes but there was a slow temperature rise in the hand to a maximum below the adult normal.

Second Test after Three and a Half Weeks. An adult response in all three limbs.

SUMMARY. A moderately severe cretin who gave no response in the feet and a subnormal response in the hand but after three and a half weeks of treatment showed normal responses in all three limbs.

Case 6. P.T. was aged 7 years at the time of the test.

Third child. Full-term. Normal delivery. Birth weight 7 lb. 8 oz. In the first year of life had been slow in feeding but a 'model baby' otherwise, not crying. Since then had been slow in acquiring motor facilities and in movement, had been constipated, and no teeth had erupted until the age of 3 years. She was given thyroid intermittently from the age of 6 months to 1 year and continuously since then in a dose of grain ⅛-¼ daily. She had received none for one month before examination and testing.

EXAMINATION. A small, pale, girl with mild but definitely cretinous features. Skin dry and coarse. Neck short. Abdomen protuberant with a small umbilical hernia. Slow in movement and cerebration. Under height (8 in.). Subnormal temperature. Hypotensive (75/55 mm. Hg).

INVESTIGATIONS. Haemoglobin 89%, bone age 'on the low side of normal', serum cholesterol level 332 mg. per 100 ml., E.C.G. normal, I.Q. 78%.

PROGRESS AND TREATMENT. Thyroid was given at first in a dose of grain ¾ daily and this was gradually increased over the next month to grains 2 daily. On the latter dose she was more alert, her movements were quicker and her constipation had disappeared.

REFLEX VASODILATATION TESTS. The results are shown in Table 1.

First and Second Tests before the Start of Treatment. An adult type of response in all limbs.

SUMMARY. A cretin who had been treated with an inadequate dose of thyroid from the age of 6 months, she showed some but not all of the features of hypothyroidism. Her vasodilatation response was normal even after four weeks without thyroid treatment.

Discussion

The results in this small series seem quite definite (Table 2). None of the responses were normal for the age in the five untreated cases. Two of the three severe cases showed no response at all, and the third showed a slow and inadequate one. The moderately severe case showed no response in the feet and a subnormal one in the hand. The mild case gave a result nearest to the normal, although it cannot be regarded as normal since the response improved on treatment. Only the child who had been treated for most of her life with thyroid produced normal responses.

TABLE 2
SUMMARY OF RESULTS

Case	Initial Test	Subsequent Tests (Weeks after Start of Treatment) 1	2	3	4	8	11
A.R.	A		P	P	P		N
B.M.	A			P		N	
G.E.	P			N			
S.G.	P				N		
C.C.	A (feet)			N			
P.T.	N						

A = absent response
P = partial response
N = normal response

In all cases the response became normal during replacement therapy.

Before concluding that in cretinism the vasodilatation reflex is in abeyance, however, two other possibilities must be considered:

(1) The inadequate temperature responses are due

to the thick skin and subcutaneous tissues of the cretin. This explanation might well be true in Case S.G., where there was no delay but the maximum temperature was lower before treatment than afterwards. However, it could not explain the complete failure of the temperature to rise in the three cases A.R., B.M. and C.C. In addition, the fact that in Case S.G. the timing of the response was approximately the same before and after treatment suggests that the insulating effect of myxoedematous tissue is slight.

(2) The peripheral vascular tree is inadequately developed, so that a normal reflex is unable to evoke a normal temperature response because the arterioles or arteriolovenous anastomoses are few or absent. In the myxoedematous adult the skin capillaries have been shown to be few, narrow, and straighter than normal (Zondek, Michael and Kaatz, 1941), and it is likely that this applies to the hypothyroid child also. Information about the state of the arterioles or arteriolovenous anastomoses has not been found, but it is quite likely that they also are reduced in number. This explanation would account for the small difference in the response before and after treatment in Case S.G. but, again, it would not account for the total lack of response in the three patients mentioned. It also seems unlikely that such a complete development of the peripheral vascular tree as would be required to explain the facts could occur in such a short time as three and a half weeks (Case C.C.).

Assuming, then, that the results indicate a failure of the reflex, there are several hypotheses which require consideration. The first is that the response is inhibited by sympathetic overaction. In a disease where all functions are apparently depressed it would be strange if there were any function which was overactive, and this explanation therefore seems unlikely on theoretical grounds. Moreover, it has been shown both in animals and man that sympatheticomimetic effects are enhanced in hyperthyroidism and depressed in hypothyroidism (McCarrison, 1917; Lyon, 1923; Blau and McNamara, 1930). Finally, there are none of the signs of generalized sympatheticotonia in the cretin such as are found in pink disease where this explanation is likely (Vulliamy, 1952; Bower, 1954). The response to ganglion-blocking agents would have proved or disproved this point. If one of these drugs, administered at the same time as the arm was first immersed in warm water, had had no effect, excessive vasoconstrictor tone would have been disproved. However, it was not considered justifiable to perform this experiment, since the drugs could have had no possible therapeutic value.

Interruption of the reflex pathway at any point would explain the results and it is therefore necessary to consider the anatomy of the reflex pathway, which is nowadays clearly delineated There are two afferent routes from the heated limb. The more important and certainly more easily demonstrated pathway is the venous one (Pickering, 1932; Fatherree and Allen, 1938; Richards, 1946; Snell, 1954). Warmed venous blood travels centripetally and acts upon a thermosensitive centre in the hypothalamus, which is the central relay station of the reflex (Duthie and Mackay, 1940; Fulton, 1943). There has been much less agreement about the existence of an afferent nervous pathway, but recently its existence seems to have been demonstrated conclusively (Kerslake and Cooper, 1950); it is probably situated in the sympathetic system (Cooper and Kerslake, 1953). The efferent pathway is the sympathetic nervous system (Lewis and Pickering, 1931; Freeman, 1935; Fatherree and Allen, 1938; Richards, 1946) and recently it has been shown that the efferent 'stimulus' is entirely inhibitory, i.e., a cessation of the vasoconstrictor impulses normally passing down the sympathetic nerves (Arnott and Macfie, 1948; Gaskell, 1954). The effector organs themselves are the 'strong arterioles' of Lewis and probably the arteriolovenous anastomoses (Grant and Bland, 1931; Barcroft, 1956).

Considering each of these sites in turn as a possible cause of the absence of response, both afferent and efferent sides of the arc can be easily eliminated. There is no reason to think that warmed blood does not travel to the hypothalamus as in the normal. Indeed, the rapid rise of rectal temperature by 0·5° C. in Case A.R. (Fig. 2) is evidence that it does so. It is most unlikely that the fault lies in a functionless afferent nervous pathway, for this is generally considered to be much less important than the venous pathway. Indeed, for many years its existence was denied. Disturbance of the efferent neurones might seem more likely on first consideration, for a reduction in the excitability of peripheral nerves in hypothyroidism has been demonstrated (Horsten and Boeles, 1949). However, since it is now known that the efferent 'stimulus' is entirely inhibitory, no hypothesis involving neuronal depression at this site can stand.

Depression of hypothalamic function is an attractive possibility, for we know that there is a depression of cerebral function in the cretin, and in animal experiments this has been correlated with immaturity of the sensorimotor cortex in relation to the development of both nerve cells (Eayrs and Taylor, 1951)

and blood vessels (Eayrs, 1953). And a reduction in blood flow and oxygen uptake in the brains of cretins has been demonstrated (Himwich, Daly, Fazekas and Herrlich, 1942).

Finally, the peripheral vessels themselves may be unable to dilate, although the 'stimulus', the cessation of vasoconstrictor impulses, reaches them. Possibly the walls of the arterioles and/or arteriolovenous anastomoses are the seat of myxoedematous change so that dilatation is physically impossible or possibly local thyroid hormone is necessary for the response to occur.

Whatever the exact mechanism, it is justifiable to conclude from the results that reflex vasodilatation is depressed or absent in cretinism. Although the acral coldness and cyanosis may in part be due to diminished cardiac output, low tissue metabolism and possibly a reduction in the number of peripheral vessels, it is probably the failure of the peripheral vessels to respond reflexly to warming elsewhere which is chiefly responsible.

Summary

The well-known feature of cretinism, poor peripheral circulation, is considered in the light of possible immaturity of the vasodilatation reflex. Five cases of untreated cretinism are described, together with their incomplete or absent reflex response to warming of one limb; the appearance of a normal response during thyroid medication is demonstrated in all. A sixth case which had been treated with thyroid for long periods gave a normal response. The possible sites of disturbance of the reflex arc are considered, and reasons are given for postulating that either the hypothalamus or the peripheral vessels themselves are at fault. Whatever the precise anatomical site, the poor peripheral circulation in cretinism is probably, in part at least, due to a failure of skin vessels to dilate in response to warming elsewhere.

I wish to thank Professor J. M. Smellie, Dr. Victoria Smallpeice, Dr. H. L. Ellis and Dr. W. H. P. Cant for the opportunity to investigate patients under their care. Fig. 1 is reproduced by permission of the editors of *The Quarterly Journal of Medicine*.

References

Arnott, W. M. and Macfie, J. M. (1948). *J. Physiol.* (*Lond.*), 107, 233.
Barcroft, H. (1956). In *Peripheral Vascular Disorders*, p. 144. Ed. Martin, P., Lynn, B. B., Dible, J. H. and Aird, I. Edinburgh.
Blau, N. F. and McNamara, H. (1930). *Proc. Soc. exp. Biol.* (*N.Y.*), 27, 997.
Bower, B. D. (1954). *Quart. J. Med.*, 23, 215.
—— (1956). M.D. Thesis, University of Birmingham.
Cooper, K. E. and Kerslake, D. McK. (1953). *J. Physiol.* (*Lond.*), 119, 18.
Duthie, J. J. R. and Mackay, R. M. I. (1940). *Brain*, 63, 295.
Eayrs, J. T. (1953). *Nature* (*Lond.*), 172, 403.
—— and Taylor, S. H. (1951). *J. Anat.* (*Lond.*), 85, 350.
Fatherree, T. J. and Allen, E. V. (1938). *Arch. intern. Med.*, 62, 1015.
Freeman, N. E. (1935). *Amer. J. Physiol.*, 113, 384.
Fulton, J. F. (1943). *Physiology of the Nervous System*, 2nd ed., pp. 235-6, 251. New York.
Gaskell, P. (1954). Quoted by Barcroft, H. in *Peripheral Vascular Disorders*, p. 137. Ed. Martin, P., Lynn, R. B., Dible, H. J. and Aird, I. Edinburgh.
Gibbon, J. H. and Landis, E. M. (1932). *J. clin. Invest.*, 11, 1019.
Grant, R. T. and Bland, E. F. (1931). *Heart*, 15, 385.
Himwich, H. E., Daly, C., Fazekas, J. F. and Herrlich, H. C. (1942). *Amer. J. Psychiat.*, 98, 489.
Horsten, G. P. M. and Boeles, J. T. F. (1949). *Arch. int. Pharmacodyn.*, 78, 93
Kerslake, D. McK. and Cooper, K. E. (1950). *Clin. Sci.*, 9, 31.
Lewis, T. and Pickering, G. W. (1931). *Heart*, 16, 33.
Lyon, D. M. (1923). *Brit. med. J.*, 1, 966.
McCarrison, R. (1917). *The Thyroid Gland in Health and Disease*, p. 177. London.
Pickering, G. W. (1932). *Heart*, 16, 115.
Richards, R. L. (1946). *The Peripheral Circulation in Health and Disease*. Edinburgh.
Snell, E. S. (1954). *J. Physiol.* (*Lond.*), 125, 361.
Talbot, F. B. (1931). *Amer. J. Dis. Child.*, 42, 965.
Vulliamy, D. G. (1952). *Lancet*, 2, 1248.
Wilkins, L. (1950). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 1st ed., p. 70. Springfield, Ill.
Zondek, H., Michael, M. and Kaatz, A. (1941). *Amer. J. med. Sci.*, 202, 435.

MONGOLISM IN BOTH OF TWINS OF OPPOSITE SEX

BY

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Mongolism in both members of a twin pair is a rarity. In all recorded cases where the twins have been considered to be monozygous both have been affected. Among dizygous pairs the great majority are discordant for mongolism but mongolism in both of twins of the same sex although considered to be dizygous has been recorded (Russell, 1933; MacKaye, 1936; Jarvis, 1943). There is no satisfactory report of monozygous twins in which only one of the pair was a mongol, neither is there a record of a pair of twins of opposite sex both of whom were mongols. The purpose of this paper is to put on record what would appear to be the first report of mongolism in both of twins of opposite sex.

Case Reports

Parents' Histories. The parents of the twins are not related. Their mother was 41 years and their father 40 years of age at the time of their birth.

The mother was one of a family of eight children, five brothers and one sister living. Her Wassermann reaction is negative. She married at the age of 25 years. The father has eight brothers and one sister, all of whom are well. He served in the army during the Second World War, but was discharged 'because of nerves'. Both parents are good looking and of normal intelligence. No history of mongolism or mental defect was discovered on enquiry into either side of the family. There is a history of twinning on the mother's side, but none in her husband's family.

Previous and Present Obstetric History. The mother had had six previous successful pregnancies, in 1939, 1940, 1941, 1945, 1947 and 1949. All these children are well with no evident congenital physical or mental abnormality. They all have a satisfactory school record.

In 1951, after an abortion at 11 weeks, a dilatation and curettage was carried out. Because of severe headache, at this time, she was examined by a hospital physician but no abnormality was found and her symptoms were attributed to an anxiety state. A further curettage was performed in October, 1952, because of chronic cervicitis. After this operation the menses were regular every three weeks, until August, 1953, when her eighth pregnancy began. At the 27th week she was admitted to hospital because of epigastric pain which settled spontaneously. The presence of a twin pregnancy was confirmed by radiology. There was no further complication of pregnancy, the blood pressure did not rise above 150/80 mm. Hg, there was no albuminuria and only slight swelling of the ankles. There was no antepartum haemorrhage.

Labour occurred spontaneously at the 36th week. The first child, a male, was delivered by the vertex. His condition was satisfactory. The second child, a female, was delivered by forceps five hours later. This baby was limp but recovered quickly. The first placenta came away readily, but the second was adherent and had to be removed manually. Both placentas and membranes were normal. Both infants were recognized as mongols at birth.

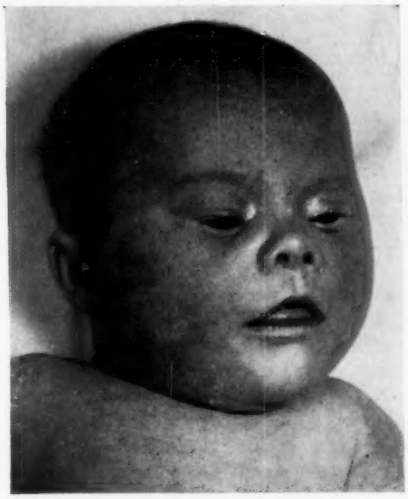

FIG. 1.—Female twin at 7 weeks.

Female Twin M.M., the girl, weighed 2·27 kg. (5 lb.) at birth. She showed the following physical stigmata suggestive of mongolism. The skull was brachycephalic, the back of the head flat, the bridge of the nose flat with forward-pointing nostrils. The palpebral fissures were slanting with small bilateral epicanthic folds. The hair was soft and brown. The irides were greyish-blue with radial white streaks. The mouth was kept open and the tongue frequently protruded. Her hands were short and

broad and both fifth fingers short and incurved. The palmar creases on the left hand were normal, but a typical four-finger line was present on the right palm.

FIG. 2.—Male twin at 7 weeks.

FIG. 3.—Mongol twins at 7 weeks of age.

The feet were small and clumsy, showing bilaterally a wide gap between the first and second toes, with a well defined crease. There was marked hypotonia and hyperflexibility of the joints. A nasal discharge and a mild conjunctivitis developed within a few weeks of birth. When seen at 7 weeks of age she appeared even more clearly a mongol. A radiograph of the chest and an electrocardiogram showed no abnormality. She had not smiled but is said to have done so at the age of 3 months when she had gained some control of head movement. When 5 months old she developed a cough which became progressively worse and at 6½ months she was admitted to this hospital in a critically ill state and died shortly after admission.

Male Twin. J.M. weighed 2·78 kg. (6 lb. 2 oz.) at birth and showed many of the physical features associated with mongolism similar to those of his sister. He, however, had also a precordial systolic murmur, and radiological and electrocardiographic examinations at 7 weeks showed enlargement and hypertrophy of the right side of the heart. When examined at the age of 20 months he had the typical appearance and behaviour of a mongol. His weight was 10·30 kg. (22 lb. 14 oz.). The circumference of the skull was 46·35 cm. (18¼ in.) and the cephalic index 0·98. His head showed brachycephaly with a flat occiput and absence of bony prominences. His nose was flat with nostrils facing forwards. The palpebral fissures were oblique and narrow. Slight bilateral epicanthus, slight rhinitis and blepharitis were present. The irides were greyish-blue and speckled. The mouth was kept open with protruded and slightly furrowed tongue. His right ear was prominent with a poorly formed lobule. His hair was smooth and soft and reddish. The neck was short and broad. The hands were short and broad with incurved fifth fingers. There was only one flexion crease on the right fifth finger, associated with a vestigial phalanx visible radiologically. The main transverse creases on both palms were not true four-finger lines, as they showed a slight break in the mid-portion. The feet were small and clumsy, the first and second toes being widely separated on both sides with a plantar crease. There was marked hypotonicity as well as hyperflexibility of the joints. The testicles were palpable in the scrotum. He could sit up unaided at about 1 year and began to stand with support about that time. He walked at 16 months but when seen at the age of 2 years and 3 months he could just get up off the floor into the standing position without aid. He cannot run more than a few steps without falling. He cannot crawl upstairs. He cannot feed himself. He will not play with toys, will not concentrate, has no interest in pictures and is rather destructive. He follows his mother about the house all day like a dog. Although he said 'Da-Da-Da' at 1 year, there is no increase in speech since. He cut his first teeth, which were molars, at 14 months and further dentition is delayed showing irregular sequence of eruption. Assessment of his mental state was made by the child psychologist of this hospital on two occasions using the Cattell Infant Intelligence Scale. At 1 year 7 months his mental age was about that of an 8-month child and at 2 years 2 months his mental age was about that of 9 months, which gives an I.Q. of 34. The psychologist reports: 'I am not in any doubt but that he is a mental defective, and although his I.Q. may be a little higher than 34, I would expect that he would fall into the high-grade imbecile range.' When assessed on the Vineland Social Maturity Scale, which is designed to be an assessment of the degree to which a child has

TABLE 1.
BLOOD GROUPS OF PARENTS AND OF MONGOL TWINS

	A B O	Rh Genotype	MN	S	P	Lu	Kell	Le^a	Le^b	Fy^a
Father	O	cde/cde	M	+	+	−	−	+	−	−
Mother	B	CDe/CDe	N	−	+	−	−	+		+
Male twin ..	B	CDe/cde	MN	−	+	−	−	+	−	+
Female twin ..	B	CDe/cde	MN	−	+	−	−	+	−	−

been socially trainable and has achieved independence, he is about the level of 1 year 5 months at the age of 2 years 2 months.

The blood groups of both mongols and their parents are shown in Table 1.

Discussion

Since 1866 when Langdon Down first recognized mongolian idiocy as a specific condition, there has been much discussion as to the probable aetiology of this abnormality. The relative importance of genetic factors within the ovum (either inherited or the result of mutation) as compared with environmental factors affecting the fertilized ovum have been debated strongly with much evidence brought forward in support of both sides. Only one fact, however, has been clearly established, namely, that the incidence of mongolism increases with increasing maternal age (Penrose, 1954a and b).

Many investigators have naturally turned to twin studies which might be expected to give useful evidence in determining the relative importance of heredity and environment by comparison of incidence in monozygous and dizygous pairs. The use of this method, however, has been hampered by the inadequate detail of many reports in which the diagnosis of either mongolism or zygosity, or both, is not supported by sufficient evidence. It has become increasingly evident how difficult it is to establish a positive diagnosis of monozygosity in twin pairs and several criteria have to be examined in each case. Assessment of single features such as placental membranes, finger prints, etc., may be misleading.

The diagnosis of dizygosity in the present pair is made clear by the difference in sex. With young infants, however, it is less easy to establish a positive diagnosis of mongolism and this applies particularly to the proof of mental defect which is generally held to be an essential element. In the present case histories, therefore, stress has been laid on the physical features of mongolism.

In the case of the female twin, who died at the age of 6½ months, the diagnosis rests on the clinical impression of all who saw her and which we hope is conveyed in the photographs reproduced here. She was seen during life by several physicians, all of whom accepted the diagnosis. Slides of a series of photographs have been presented before a meeting of the Scottish Paediatric Society. The meeting agreed that she had the characteristic features of mongolism.

The surviving male twin was shown to the Society and again the diagnosis was unanimously accepted. He has now lived long enough for a firm diagnosis of mental defect to be established. We therefore feel justified in our assertion that these twins were of opposite sex, were therefore dizygous, and were both mongols.

Summary

The presence of mongolism in both of twins of opposite sex is recorded. There is no previous record in the literature of this occurrence.

Our thanks are due to Miss Jessie F. Reid, formerly psychologist, Department of Psychological Medicine, Royal Hospital for Sick Children, Edinburgh, for her reports.

REFERENCES

Down, J. Langdon H. (1866). *London Hosp. Rep.*, **3**, 259.
Jervis, G. A. (1943). *Amer. J. ment. Defic.*, **47**, 364.
MacKaye, L. (1936). *Amer. J. Dis. Child.*, **52**, 141.
Penrose, L. S. (1954a). *Lancet*, **2**, 505.
—— (1954b). *Ann. N.Y. Acad. Sci.*, **57**, 494.
Russell, P. M. G. (1933). *Lancet*, **1**, 802.

CYANOTIC ATTACKS IN NEWBORN INFANTS

BY

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By the term 'cyanotic attacks in newborn infants' I mean sudden attacks of cyanosis, lasting from a few moments up to half an hour, in children whose colour was previously normal, and whose colour returns to normal in atmospheric air after the attack. I do not include the sudden development of cyanosis in a baby who remains blue until death.

In an extensive search of the literature I was unable to find any paper on the subject, though a number of papers concerning cyanosis or other neonatal problems mention briefly the occurrence of short periods of cyanosis. I could not find the term 'cyanotic attacks' or 'blue attacks' in the index of any of 14 recent British and American text-books of paediatrics: yet every midwife and every paediatrician responsible for the care of newborn babies is fully conversant with the frequency and alarming nature of these attacks.

The most comprehensive statement about cyanotic attacks was that by Crosse and Young (1954). They wrote that the attacks

> 'may be due to intracranial birth injury, pulmonary atelectasis, hyaline membrane, congenital malformation of the respiratory tract, or of the diaphragm or of the heart, obstruction of the respiratory tract by aspiration, infection, over- or under-heating, too much handling, or to overfeeding which causes abdominal distension and hence respiratory embarrassment. The differential diagnosis of the cause of the attack is often difficult, but if there are no signs of developmental defects, it should be assumed that the attacks are functional in origin.'

Clein (1929) thought that intermittent cyanosis in premature babies was mainly due to cerebral haemorrhage. Capper (1936) wrote that 'an infant whose cyanosis is intermittent rather than continuous is usually suspected of suffering an intracranial injury'. Phillips (1936) wrote that 'frequent cyanotic attacks are the rule with premature babies. They occur without apparent cause. Respirations may cease for as long as one minute. An attack may come on following a feed, the full stomach interfering with the action of the diaphragm'. Bonar (1937) suggested that intermittent cyanosis is likely to be due to increased intracranial pressure, atelectasis, or obstruction of the air passages by mucus. Harris (1950) wrote that the commonest cause of respiratory obstruction in newborn babies was mucous plugs in the nares.

The Present Study

This study is based on 170 babies who had cyanotic attacks in the newborn period in the Jessop Hospital for Women at Sheffield in the eight-year period 1949 to 1956. In the last six years there was an average of 26 cases each year. The study includes babies born on district and admitted to the hospital. The average number of live-born babies delivered each year in the hospital during this period, or admitted from the district, was 1,680. During the latter part of the time we used a detailed proforma in each case.

Results

Birth Weight. One hundred and three of the babies (60%) were premature (Table 1). One baby was post-mature and died from cerebral haemorrhage. During this period 10% of the babies in the hospital were premature.

Day of Onset of Cyanotic Attacks. In 40% of the babies the attacks began in the first 24 hours, and in 72% in the first three days (Table 2). Six babies had their first cyanotic attack after the first week, the oldest baby (premature) having an attack on the 27th day after birth. There seemed to be no relationship between certain prenatal factors (to be discussed below) and the day of onset of the cyanotic attacks.

The Frequency of Attacks. Forty per cent. of the babies had only one known cyanotic attack, 32% had two to four attacks and 28% had five attacks or more.

Prenatal Factors. Table 3 shows the incidence of maternal illness. Toxaemia is defined as the

TABLE 1

BIRTH WEIGHT AND MORTALITY OF BABIES WITH CYANOTIC ATTACKS COMPARED WITH MORTALITY OF OTHER BABIES IN THE HOSPITAL

Birth Weight (lb. oz.)	Babies with Cyanotic Attacks*		Babies without Cyanotic Attacks, 1951-1955*	
	Total	Mortality (Percentage)	Total	Mortality (Percentage)
2 8 or less	19	84·2	35	74·3
2 9 to 3 8	27	66·6	86	26·7
3 9 to 4 8	29	68·9	184	12·5
4 9 to 5 8	26	61·6	474	2·9
Premature babies not weighed ..	2	—	—	—
Total premature babies ..	103	70·0	779	10·9
Total full-term babies	57	14·9	7,481	0·7

* Includes previable births (26 or 27 weeks' gestation), and all congenital anomalies, including anencephaly.

The figures include babies admitted to the hospital because of illness.

occurrence after the 26th week of any two of the following: (1) A blood pressure of over 140 mm. systolic or 90 mm. diastolic; (2) 50 mg. % or more of albumin in the urine; (3) non-dependent oedema.

Forty-six mothers (27%) had toxaemia, 18 (11%) had hypertension without toxaemia, and 25 others (15%) had antepartum haemorrhage (Table 3). In addition one mother was very ill with toxic hepatitis.

The Jessop Hospital at Sheffield is a teaching hospital and takes a large proportion of abnormal cases, but the high incidence of toxaemia, hypertension and antepartum haemorrhage is notable. It might be thought that the high incidence of toxaemia in mothers of infants with cyanotic attacks could be explained by the frequency with which toxaemia causes premature delivery (Table 4), but the incidence of prematurity (60%) in babies with cyanotic attacks was exactly the same whether their

TABLE 2

DAY OF ONSET OF CYANOTIC ATTACKS

Day of Life	Total Number	Percentage of Total
1	68	40
2	29	17
3	25	15
4	16	9
5	8	5
6	13	8
7	3	2
8 days or more	6	4

TABLE 3

PRENATAL FACTORS IN CYANOTIC ATTACKS RELATED TO ILLNESS DURING PREGNANCY

Illness	Number	Total
Toxaemia	39	
Toxaemia with antepartum haemorrhage	4	
Toxaemia with pyelonephritis, anaemia, diabetes	1 each	46 (27·1%)
Hypertension without toxaemia ..	12	
Hypertension with antepartum haemorrhage	2	
Hypertension with anaemia, hydramnios, hyperemesis, mitral stenosis ..	1 each	18 (10·6%)
Chronic nephritis	1	1
Antepartum haemorrhage (apart from above)	22	
Antepartum haemorrhage at 3 months,		
Antepartum haemorrhage at 3 months with pulmonary tuberculosis		
Antepartum haemorrhage at 5 months	1 each	25 (14·9%)
Hydramnios (apart from above) ..	4	4
Diabetes (apart from above)	3	3
Anaemia		
Anaemia with pyelonephritis, mitral stenosis	1 each	3
Mitral stenosis with hyperemesis, congenital heart disease, severe toxic hepatitis and pyelonephritis, pyelonephritis with disseminated sclerosis, syphilis, haemorrhage due to papilloma of bladder, bicornuate uterus	1 each	7

mothers had toxaemia or not. Analysis of a three-year period (1953-55) showed that of 597 babies born to mothers who had toxaemia, 22 (3·7%) had cyanotic attacks. During that period 4,471 non-toxaemic mothers gave birth to live-born babies, but only 61 (1·3%) had cyanotic attacks. Hence there is an association between toxaemia in the mother and cyanotic attacks in the baby, and this is unrelated to prematurity. There is the same association between cyanotic attacks in the baby and hypertension or antepartum haemorrhage, and the same arguments apply. For instance, during the same period, 203 mothers who had had antepartum haemorrhage (without toxaemia) gave birth to live-born babies: 6·1% of these had cyanotic attacks. During that period 4,865 mothers gave birth to live-born babies without having had antepartum haemorrhage, and of these 1·2% had cyanotic attacks.

There was no relationship between the day of

TABLE 4

RELATIONSHIP OF CERTAIN PRENATAL CONDITIONS WITH PREMATURITY IN BABIES HAVING CYANOTIC ATTACKS

Condition	Total	Premature	Full-term Babies
Toxaemia	46	28 (60·8%)	18
Nephritis, chronic ..	1	1	0
Hypertension	18	9 (50·0%)	9
Antepartum haemorrhage	24	18 (75·0%)	6
Other conditions ..	81	47 (58·0%)	34
Total	170	103 (60·6%)	67

onset of the cyanotic attacks and the prenatal factors above, or between the age of the mother and the incidence of cyanotic attacks.

Eighteen of the babies with cyanotic attacks were twins. In no case did both twins have cyanotic attacks.

One child had congenital stippled epiphyses and another had hydrocephalus. Six were notably oedematous at birth, three of these being born to mothers with toxaemia or hypertension.

Natal Factors. One hundred and thirty-four of the babies were vertex deliveries, 15 of them being delivered by forceps: 24 were delivered by caesarean section; 12 were breech presentations.

Forty-one (24%) of the babies had grade 2 or 3 asphyxia, using Flagg's classification. In 1955 and 1956, 4·6% of the babies born in the hospital had grade 2 or 3 asphyxia, and 16 of the 39 babies (41%) born in those years who had cyanotic attacks had grade 2 or 3 asphyxia.

Postnatal Conditions. Twitching or convulsions occurred in 27 of the babies. In only four of these children was there twitching at the time of a cyanotic attack, on one or two occasions only, and in all these children several cyanotic attacks occurred without twitching being observed. In all the others the twitching or convulsion bore no time relationship to the attacks of cyanosis.

Mortality and Findings at Necropsy. Eighty-two of the children died (48%), and necropsies were carried out on 72 of them. The principal finding at necropsy was severe atelectasis, with or without hyaline membrane, in 36% of the babies. For comparison, I studied the necropsy findings in 115 consecutive babies who had died without having cyanotic attacks, and of whom 67% were prematurely born: 29% of these showed atelectasis as the principal finding—a very similar figure.

The second commonest finding at necropsy was gross cerebral haemorrhage in 33% of the babies. This figure is precisely the same as that in the babies who died without cyanotic attacks.

Other findings consisted of marked cerebral oedema alone, tracheo-oesophageal fistula (two of which died after operation), gross pulmonary haemorrhage and infections. It was notable that only two babies had gross congenital heart disease whereas in the control group there were eight of these in the 115 babies.

TABLE 5
FINDINGS AT NECROPSY IN 72 BABIES SUFFERING FROM CYANOTIC ATTACKS

Necropsy Findings	Number	Total
Atelectasis with or without hyaline membrane	15	
Atelectasis with cerebral oedema	10	
Atelectasis with massive pulmonary haemorrhage	1	26 (36%)
Gross cerebral haemorrhage alone	19	
Gross cerebral haemorrhage with pulmonary haemorrhage	1	
Gross cerebral haemorrhage with atelectasis	4	24 (33%)
Infections:		
E. coli septicaemia	2	
E. coli meningitis	1	
Pneumococcal meningitis	1	
Bronchopneumonia	1	5
Cerebral oedema alone	3	
Cerebral oedema with liver haemorrhage	1	4
Anomalies of oesophagus	3	3
Pulmonary haemorrhage	2	2
Congenital heart disease	2	2
Kernikterus with atelectasis	1	1
Micrognathia with prematurity	1	1
Sclerema	1	1
Nil gross	3	3
Total	72	72
Percentage premature 84		

Prognostic Features. These can be related to weight at birth, day of onset, frequency of attacks, and twitching and convulsions.

WEIGHT AT BIRTH. The mortality in the prematurely born babies with cyanotic attacks was 70%, as compared with 15% in the full-term babies (Table 1). This corresponds with figures of 10·9% and 0·7% respectively in all other prematurely born and full-term babies born in the hospital or admitted because of illness from outside. In all cases previable babies and gross congenital anomalies, such as anencephaly, are included.

DAY OF ONSET. Of those who had the first cyanotic attack in the first three days after birth, 47% recovered: of those who had the first attack on the fourth day or later 61% recovered.

FREQUENCY OF ATTACKS. Of those who had one to four known attacks, 58% recovered as compared with 32% of those having five or more known attacks.

ASSOCIATION WITH TWITCHING OR CONVULSIONS. Of the 27 children with cyanotic attacks and convulsions, eight recovered and 19 died. Eight of the latter were found at necropsy to have cerebral haemorrhage, three had severe cerebral oedema, two had atelectasis, and two congenital heart disease. Two of these eight survivors have been followed up for five years and one is mentally defective.

Difficulties in the Diagnosis. It is almost certain that in many of the babies a cyanotic attack was due to obstruction of the respiratory passages by mucus, liquor, meconium, vomitus or milk. This was thought to be the only cause in 29 babies who

recovered. One cause of difficulty in this connexion is the fact that the newborn baby often fails to open his mouth to breathe when his nose becomes blocked. In 11 other babies the cyanotic attacks occurred during a feed, and it would be reasonable to suppose that the attack was due to the inhalation of milk, though this was not confirmed by aspiration. The majority, however, of the babies who had their first cyanotic attack in the first two days had not at the time begun to receive food by mouth (most of the babies being prematurely born), so that there could be no connexion between feeds and the attacks.

The fact that mucus or vomitus was aspirated from a baby in the attack, and that the baby recovered after such aspiration, by no means proved that the attacks were due to respiratory obstruction due to inhalation of those materials. In several babies one attack occurred during a feed, while other attacks in the same baby bore no time relation to feeds. For instance, a baby's first cyanotic attack occurred during a feed, and several further attacks were unrelated to feeds. At necropsy a massive cerebral haemorrhage was found. In several other babies a considerable amount of mucus was extracted during one cyanotic attack, while in other attacks little was obtained, and not enough to account for the attack. In one child the first attack occurred in a feed, and was ascribed to inhalation of food, while four further attacks appeared to be related to attacks of apnoea without respiratory obstruction. A premature baby had his first cyanotic attack at 30 hours, having been previously well, and much mucus was aspirated, after which he recovered. He died the same day from pneumococcal meningitis. A 2 lb. baby had an attack during a tube feed, having been previously well. He died the same day of *E. coli* septicaemia.

Many of the attacks were probably due to unexplained phases of apnoea. I saw one baby have repeated attacks of cyanosis due to apnoea without respiratory obstruction. He responded repeatedly to gentle stimulation and survived.

Discussion

The obvious difficulty of determining the cause of cyanotic attacks during life, together with a striking absence of literature on the subject, led me to determine some facts about the condition. I am aware, however, that many questions have been left unanswered. It is obvious that many attacks were simply due to temporary respiratory obstruction; it is equally clear that many were not. It is likely that many of the attacks were due to apnoea without respiratory obstruction, but the reason for the attacks of apnoea is not known. Phasic respiration is common in healthy premature babies, and in some the irregularity of respiratory rhythm is exaggerated. Miller (1957) in his paper on respiratory function in the newborn found that attacks of apnoea and cyanosis were almost confined to babies, premature or full-term, in whom there was a notable rise of respiratory rate after the first hour from the figure of about 40 found in healthy babies to a figure of 60 or so. When the respiratory rate remained fairly constant at about 40 per minute, no respiratory problems were encountered. All the attacks of apnoea and all the deaths occurred in babies whose respiratory rate rose to the region of 60 after the first hour. Miller regarded a progressive fall of the respiratory rate in those babies as a bad sign; he found that if the respiratory rate fell below 20 per minute in a small premature baby survival was unlikely.

It would be easy to confuse a cyanotic attack with a convulsion, but in our cases we found the association unusual. An occasional baby had both cyanotic attacks and convulsions, but more often than not it would have twitching without a cyanotic attack or a cyanotic attack without a convulsion. There was a high incidence of severe atelectasis or of gross cerebral haemorrhage at necropsy, but it is interesting to note that there was almost exactly the same incidence of these conditions in babies who did not have cyanotic attacks. It is commonly thought that congenital heart disease is a common cause of the attacks. Our findings show that it is a rare cause.

There seems to be a definite association between maternal toxaemia, hypertension and antepartum haemorrhage, but the reason for this is not clear. It may well be related in some way to foetal anoxia with consequent respiratory difficulties.

It may be concluded that the nature and origin of cyanotic attacks is a good subject for speculation. It is certainly a subject which will repay further observation and research.

Summary

The known facts about 170 newborn babies who had cyanotic attacks have been presented. The following are the principal findings:

(1) Sixty per cent. of the babies were premature.

(2) There was a significantly higher incidence of maternal toxaemia, hypertension and antepartum haemorrhage in mothers of babies who had cyanotic attacks than in controls. This relationship was not merely due to the higher incidence of prematurity in those conditions.

(3) Twenty-four per cent. of the babies had grade 2

or 3 asphyxia at birth as compared with an incidence of 6% in controls.

(4) Forty-eight per cent. of the babies died. In premature babies the figure was 70%, as compared with 15% in full-term babies.

(5) At necropsy 36% showed severe atelectasis, with or without hyaline membrane, and 33% showed gross cerebral haemorrhage. The corresponding figures in babies who died without cyanotic attacks were almost identical. Congenital heart disease was only a rare cause of the condition.

(6) The principal causes of cyanotic attacks were obstruction of the respiratory tract by mucus or other material, attacks of apnoea and convulsions. The reason for the attacks of apnoea is not understood.

(7) The difficulties of making a correct clinical diagnosis are emphasized, and the need for further research is indicated.

References

Bonar, B. E. (1937). *J. Pediat.*, **11**, 572.
Capper, A. (1936). *Med. Clin. N. Amer.*, **20**, 99.
Clein, N. W. (1929). *Amer. J. Dis. Child.*, **37**, 751.
Crosse, V. M. and Young, W. F. (1954). In *Diseases of Infancy and Childhood*, ed. Parsons, L. and Barling, S., 2nd ed. London.
Harris, L. E. (1950). *Minn. Med.*, **33**, 1204.
Miller, H. C. (1957). *Pediat. Clin. N. Amer.*, February, p. 17.
Phillips, S. (1936). *J. Ark. med. Soc.*, **33**, 99.

NIGHT WAKING IN EARLY INFANCY: PART I

BY

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The Problem

The tendency for babies to wake in the night is a fact frequently deplored but comparatively little studied. In ordinary social life one meets parents of children of 1 or 2 years of age who have scarcely known an unbroken night since the child was born. The experience of the longitudinal research at the Child Study Centre, confirming the relative frequency and severity of this problem, prompted the following questions:

(*a*) What is the usual pattern of adjustment to sleeping through the night, and what proportion of babies make such a normal adjustment?

(*b*) Can differences be found between cases where such normal adjustment is made within the usual time and cases where it is not, as regards (i) characteristics of the child, (ii) characteristics of the physical and social environment, (iii) characteristics of the parents?

(*c*) Can such differences be found in relation to a more general tendency to wake at night after the initial phase of adjustment?

The Literature

Theories of sleep are reviewed by Kleitman (1939). Despert (1949) surveys the studies of children's sleep up to that time, and Sperling (1949) gives the results of psychoanalytic experience. Paediatric experience in the field is distilled by Shepherd (1948) and Illingworth (1951, 1953).

Electro-encephalography reveals that delta waves, found in adults only in somnolent states, are the characteristic pattern of early infancy and first begin to lose prominence at moments when the child is attentive 'sometimes as young as 2 or 3 months' (Walter, 1956), *i.e.*, when the 'twilight state' of the newborn is giving way to a sharper demarcation between sleep and mental activity (Ribble, 1943).

That apparently unbroken stretches of sleep are not homogeneous has been demonstrated by observational studies (Buhler, 1930; Irwin and Weiss, 1934; Wagner, 1937, 1939). Aserinsky and Kleitman (1955) found a cycle of activity and quiescence averaging one hour in duration for infants of any age between 3 and 26 weeks; at the end of the 'deep sleep' phase movements of body and eye suddenly occur, at which point the child may either wake or begin a fresh sleep cycle.

Though there are wide individual variations, more sleep is taken by night than by day, and in longer spells, even in the earliest weeks (Kleitman and Engelmann, 1953). The difference increases rapidly in the first three months, then more slowly. The fact that infants fed on self-demand progressively lengthen the intervals between their night feedings (Gesell and Ilg, 1937; Marquis, 1941) is further proof that maturation plays a large part in this process. Our present purpose is to study deviations from this normal pattern of adjustment to the 24-hour cycle.

Material for the Present Enquiry

The material of the present enquiry is part of that collected on a sample of about 200 central London children who are being studied longitudinally from birth onwards at the Child Study Centre. This sample is fairly representative of the population using the National Health Service, and includes cases from each of the five major categories of the Registrar-General's classification of social class. A previous paper (Moore, Hindley and Falkner, 1954) sets out the aims and methods of the study. Sleep is only one of many topics covered in the routine interviews with mothers at the Centre. For purposes of the sleep study, the information so gained on 160 cases was supplemented in a subgroup of 45 cases (Group D) by means of home visits.

Although it is recognized that mothers vary considerably in the accuracy of their reports, it was found in general that the home visits to the subgroup, involving more detailed enquiries, confirmed the testimony given in the ordinary research programme. In addition, some 30 mothers kept daily records of the number of times their babies woke in

the night, and what was done, until they began regularly to sleep through the night.

Definitions. We are here concerned with the problem of the baby that wakes its parents in the night. Although young infants wake many times in the course of the night, often remaining quiet and content, this creates no problem, and indeed parents are generally oblivious until fussing or crying disturbs them. Again, the baby that is wakeful during the evening may create a problem for parents who feel it should be asleep or who wish to have the time to themselves; but this is a different problem.

The question of how to define the night was not easy to decide. In the end we confined our attention to cases where the baby woke and cried or fussed between midnight and 5 a.m. at least once a week.

Two aspects of the problem are to be distinguished; the age at which the child first 'settles' (starts regularly sleeping through the night, as defined above) and its general tendency to wake at night during any given period. Criteria are needed for both.

For the first we have taken the age (as estimated to the nearest week from the mother's reports) at which the child began its first period of four weeks or more of sleeping through the night, waking less than once a week.

For the second criterion (of the general tendency to wake) we have a rough estimate of the number of nights broken in the year, or any part thereof. This estimate, called the 'waking score', is only approximate, being based on such generalizations by the mother as, 'He has woken three or four nights a week for the past month or so; before that it was every night', but it does take account of fluctuations, including temporary upsets due to illness. In the case of children who were reported to wake more than once nightly (between 12 and 5 a.m.) the nightly score was multiplied for the period in question by 10/7. The first two weeks of life were excluded from these scores, since most of the infants were born in hospital, where, apart from the special conditions of the night nursery, information was available only for the subgroup. Any subsequent period in hospital, if less than four weeks, was scored as for the average of the periods immediately before and after; if longer, the child was excluded from scoring. The possible score for the whole period from two to 52 weeks of age ranges from 0 to 500 (10/7 by 350 nights).

Results

Incidence of Night Waking. The best general view of the extent of the problem can be obtained by considering the frequency of night waking age by age for the first year (Fig. 1). (Calculations of incidence are based on 104 cases comprising two sampling groups, graphed separately to show their

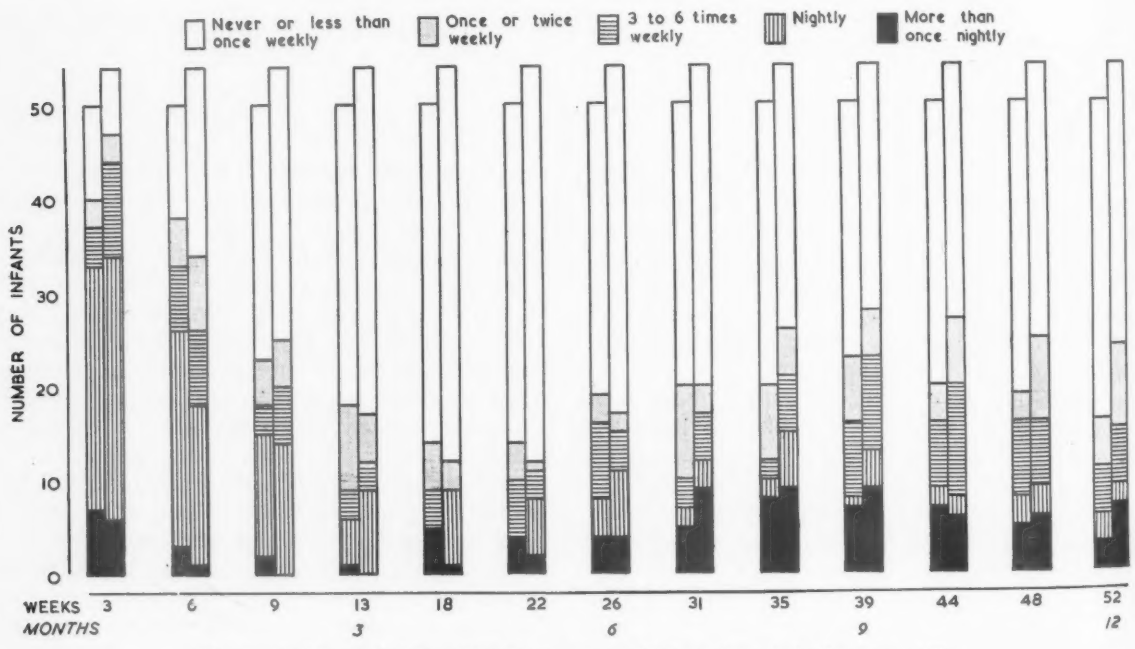

FIG. 1.—Incidence of night waking in two groups of infants through the first year of life.

TABLE 1
DISTRIBUTION OF INITIAL SETTLING AND LATER RELAPSES DURING THE YEAR

Month of Life	(*a*) First Settled				(*b*) Onset of Relapse	
	No. without Relapse	No. with Later Relapse	Total Number	Cumulative %	No.	Cumulative %
1	12	8	20	19·2		
2	18	22	40	57·7		
3	8	6	14	71·2	2	
4	5	5	10	80·8	4	5·8
5	1	1	2		3	
6	1	0	1	83·6	8	16·4
7	0	2	2		11	
8	0	1	1	86·5	7	33·6
9	1	0	1		7	
10	3	0	3	90·4	2	42·3
11	0	0	0		1	
12	0	0	0		0	
	49	45	94	90·4	45	43·2
Not settled in 1st year			10	9·6		
			104	100·0		

Information available on 104 cases.

close agreement. The remainder of the sample was excluded because enquiry as to age of settling, etc. was less specific; but the same trend emerges.)

The percentage of children waking drops steeply in the first four months, after which there is a distinct rise from 5 to 9 months, followed by a slighter drop.

To understand this curve of incidence, we need first to know how many children had never fully settled by any given age, and how many had settled but later resumed waking.

Table 1 shows the distribution of initial settling, month by month, together with the number of those settled in each month who relapsed for four weeks or more at any time during the first year.

It will be seen that about 70% of the babies had ceased waking in the night by the age of 3 months, and another 13% by the age of 6 months. Ten per cent. never settled completely at any time in the first year. Of those who had settled, almost a half reverted to night waking, and this happened largely irrespective of the age of first settling. The correlation between waking scores for the first three months and for the rest of the year, though positive and significant ($P<0{\cdot}05$, $N = 95$) is only $\rho=0{\cdot}21$. One cannot, therefore, predict the later nocturnal behaviour of a particular baby from his early sleeping.

The age of onset of relapses is given in Table 1. Evidently new causes of night waking begin to operate in a considerable number of cases between the sixth and ninth months, as Shepherd (1948) has noticed.

We may now look at some individual waking patterns. Those of Group D children are graphed in Fig. 2. It will be seen that they vary widely. It is not uncommon for a baby to sleep through the night for the first two or three weeks of his life, and then to have a short spell of waking, sometimes, but not always, beginning on discharge from the maternity ward. Of the majority who begin by waking nightly, some do so with gradually decreasing frequency; others start suddenly sleeping through, 'forgetting' to wake for their 2 a.m. feed; others again wake a little later every week; still others are erratic in their pattern.

Several of the cases toward the bottom of the chart show a period of less frequent waking in the second or third month, as though beginning the settling process, which is then interrupted by a fresh access of waking that sometimes persists for the remainder of the year. Consideration of these later disturbances will be deferred to a second paper.

In the following section we propose to examine the factors that may help or hinder the initial process of adjustment to sleeping through the night, by comparing infants who settled within the usual time with those who did not. For this purpose it was found empirically that the age of 13 weeks gave the best dichotomy. Some of the factors will also be viewed in relation to waking scores for the first three months, and where appropriate for the whole year, to take account of any general tendency to wakefulness. All differences reported in the following sections were tested for significance by the χ^2 technique, with correction for continuity in all 2×2 classifications (McNemar, 1949). ($P<0{\cdot}01$ indicates that the chances of an obtained difference being an accidental one are less than 1 in 100: such a difference is said to be significant at the 1% level.) The number of cases (N) varies with the availability of the information concerned.

Relation of Night Waking to Constitutional Factors. The sexes show no significant difference in age of first settling, but over the whole first year boys wake significantly more than girls ($P<0{\cdot}01$, $N = 104$) and this tendency is already apparent, though not statistically significant, in the waking scores for the first three months. This is consistent with Erwin's (1934) findings that girls sleep slightly longer on the average than boys; even as babies they seem less ready to wake.

Neither birth weight, nor weight at 3 months, nor weight increment over this period, shows any relationship to age of settling or to waking score for the period; nor do caliper measurements of the amount of subcutaneous fat. This is in agreement with Thompson (1936).

Developmental quotients (Griffiths, 1954) at 3 months and at 6 months both give correlations of the order of zero with age of settling.

An attempt was made to assess certain characteristics of the children by rating their behaviour on each visit to the Centre on a series of five-point scales. Four qualities which it was thought might bear on sleep adjustment were selected; activity, excitability, intensity of crying and cheerfulness, but none of the four showed any relationship to age of settling or waking score for the first three months. This, of course, does not prove the absence of a

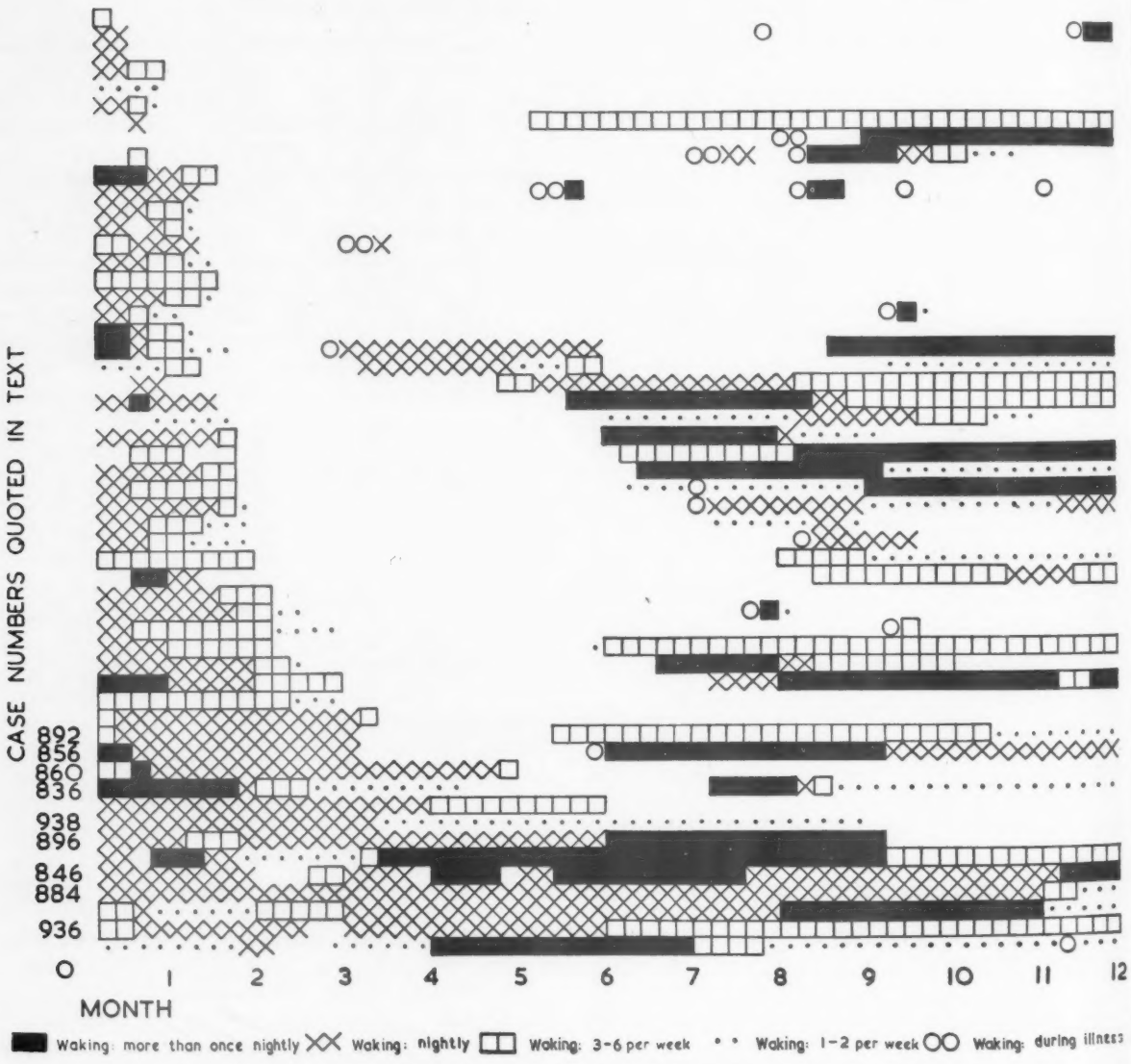

FIG. 2.—Individual patterns of night waking of 54 infants through the first year of life.

relationship, since the ratings were made in a situation which may not reveal the child as he usually is.

Many investigators have stressed the wide variation in the amount of sleep taken by different children, even in the first few days of life (Wagner, 1937). May readiness to wake at night mean merely that the child is one who sleeps less than most? The present study is not adapted to obtaining exact durations, and only 50 mothers were asked to estimate the hours their babies spent in sleep at 3 months of age. These 50 cases show a slight but consistent tendency for those who took less sleep in the aggregate to wake more at night and to settle later ($P<0{\cdot}10$). The question remains whether those who slept more by day were readier to wake in the night. There is a negative correlation ($r = -0{\cdot}34$, $N = 50$, $P\sim0{\cdot}02$) between duration of day and night sleep estimated separately, but no association between the amount of day sleep and the number of broken nights. It seems, therefore, that whereas length of night sleep may be reduced in some cases by the amount taken in the day, its continuity is not; and that it is unusual, though perhaps not unknown, for a baby under 3 months to wake regularly in the night merely because he has got into the habit of sleeping his fill in the daytime. Conversely, lack of sleep by day does not guarantee unbroken nights, as is illustrated in the case of an exceptionally wakeful baby described later (Case 936).

Relation of Night Waking to Circumstances of Birth. Asphyxia at birth, as recorded in the obstetric records, occurred in 40 infants, 19 of whom (47·5%) failed to settle by 3 months, as against only 28% of non-asphyxiated infants. The asphyxiated group continued to show a greater tendency to wake throughout the year as a whole. Both differences are significant at the 5% level.

It is recognized that the diagnosis of neonatal asphyxia is a somewhat subjective matter. The obstetric records for the whole sample were obtained from as many as 79 observers—labour ward sisters in five hospitals and midwives of two home nursing associations—of whom 33 reported asphyxia in one or more cases. Thus there is ample scope for differences in diagnostic criteria and standards. Such differences, by tending to randomize the allocation of children to asphyxiated and non-asphyxiated categories, would have the effect of obscuring any real association with an independently assessed factor such as sleeping disturbances so that the chances of this association being accidentally obtained are probably much lower than 5 in 100. The possibility of such an association first occurred to the authors while studying the histories of certain children who showed unexplained sleeping disturbances together with general unpredictability and over-reactivity. Among these children were the following (*cf.* their sleeping records in Fig. 2):

CASE 938 (boy). Severe asphyxia pallida; respiration established only after three-quarters of an hour, cried after two hours. Somewhat irritable on handling in first 24 hours. A restless and ultra-rapid feeder, prone to vomit back his feeds and difficult to settle by night and by day. Tended to wake at night, though not regularly, until 9 months.

CASE 884 (boy). Medium blue asphyxia, cord round neck. A difficult feeder whose mother found him awkward and unresponsive to cuddling after the early weeks. Continued to wake nightly to 11½ months of age.

CASE 892 (girl). Infant anaesthetized at birth (caesarian). Demands frequent feeds but does not take them well. Reported at the lying-in stage and later to be exceptionally sensitive to noise. Prone to wake at night.

CASE 846 (boy). Blue asphyxia ; responded quickly to treatment. Though generally of a happy and stable disposition, this child is subject to violent prolonged disturbances affecting feeding, sleep and general physical and emotional condition, without obvious cause. Convulsions at 6 months. Apart from three weeks in the third month, never regularly slept through night in the first year.

Preston (1945) also found that children who had suffered a mild degree of anoxia at birth showed a permanent tendency to hyperactivity and over-responsiveness, with much crying and disturbed feeding and sleep in infancy, while those with a greater depth of anoxia showed a serious degree of apathy. Darke (1944), Hellström and Jonsson (1953) and others have pointed out the possible connexion of severe asphyxia with later physical and mental impairment. Rosenfeld and Bradley (1948), studying older maladjusted children with a history of neonatal asphyxia, described a syndrome comprising unpredictable variability of mood, hypermotility, impulsiveness and short attention span with certain associated difficulties in learning. Our findings, while affording no positive proof of causal connexion, do therefore support those of other workers and strongly suggest the need for collaboration between obstetric and paediatric specialists in following up the asphyxiated neonate.

Relations of Night Waking to Temporary Conditions. It is remarkable that illnesses seem to have no lasting effect on night sleep in the first three months. Sometimes ill health may cause a few broken nights, but the sleeping pattern is resumed at once on the passing of the acute phase. Later in

the year, an illness may set in train a sleep disturbance lasting for months.

In one case circumcision at 11 weeks (done at parents' wish, not medically indicated) initiated a four-month spell of nightly waking in a baby who had settled at 6 weeks.

Unsatisfactory feeding is generally the first thing to be looked for in a wakeful baby. We find, in fact, an association at the 2% level of significance between feeding difficulties reported at 3 months and failure to sleep through the night. Where breast feeding proved unsatisfactory, weaning to bottle or complementary feeds sometimes had an immediate beneficial effect on sleep; in other cases, strengthening the formula or introducing solids settled the child. The two problems do not always coincide, however. Of 27 infants with feeding difficulties, eight slept well through the night; eight continued to wake a month or more after the feeding trouble had cleared; in the remaining 11 cases the feeding and sleeping problems cleared about the same time. There were also a number of good or excellent feeders who persisted in waking at night.

Colic, found by Illingworth (1953) to be a frequent cause of sleep disturbance between 6 and 10 p.m. during the first three months, was not identified as a cause of regular waking later in the night among our cases.

Moncrieff (private communication) has suggested that teething pains can cause much distress to infants as early as the third month, when the points of the teeth begin to stretch and finally break through the periosteum lining the outside of the jaw bone, some weeks before they cut through the gum. This may well cause spasmodic sleeping disturbances, but unfortunately our mothers were not briefed to identify the symptoms. No significant differences in age of settling were found between infants who cut their first teeth before 6 months, between 6 and 9 months, and after 9 months of age.

Other bodily discomforts such as overclothing, skin chafing, muscular discomfort from a faulty cot or mattress, etc., are listed by Shepherd (1948) as causes of restless and disturbed sleep. Systematic information on these topics is not available, though such conditions were noticed in certain individual cases.

The amount of crying reported by mothers was taken as a rough index of faultiness of adjustment, irrespective of cause. It shows a linear but statistically insignificant relationship to night waking ($P<0{\cdot}20$, $N = 105$), those who cried most tending to wake more and settle later. As an estimate of the amount of crying, mothers were asked whether the child cried—usually, sometimes, rarely or never—in each of 11 typical daily situations (the questions being spaced through the interview to reduce stereotyping of response) and her replies at both 6 weeks and 3 months were combined in a total 'crying score'. This total could be broken down into three sub-scores for crying (*a*) before and after feeds while still in the mother's arms; (*b*) when put down, left alone, or ignored; (*c*) when handled as in dressing or bathing, when taken out of the bath, and when wet or dirty. Of these three sub-scores, the first and third showed similar relationships to night waking as did the total crying score, while the second did not. From this it would appear that failure to sleep through the night may be associated with dissatisfaction around the feeding situation, or with sensitiveness to physical discomfort, but not at this early stage with a need for company. These findings should be viewed with caution in view of the possibility of chance association (P lies between 0·1 and 0·2 for (*a*), and between 0·2 and 0·3 for (*c*)), but credence is strengthened by the fact that they were first observed on two groups (105 cases), and then again on a third group (49 cases).

The average sucking time per feed, so far as mothers could estimate it, shows no relationship to the tendency to continue waking at night.

The frequency of sucking fingers or fist, again estimated by mothers, shows, on the other hand, a relationship to unbroken sleep which is probably but not certainly significant ($P<0{\cdot}10$, $N = 144$), those who sucked least numbering more persistent wakers. When finger and dummy sucking are taken together, there is a similar association at a lower level of significance. The connexion between sucking and sleep is obscure, but is frequently pointed out in psychoanalytic writings (Lewin, 1951; Sperling, 1949, Ribble, 1943). Our findings, tentative as they are, point to the desirability of further study of the inter-relationships between these factors.

Relation of Night Waking to External Stimuli. Seasonal differences of light and temperature show no relationship with age of settling, babies born at different times of year settling in equal proportions by the age of 3 months.

Nor has sharing a room any demonstrable effect on settling age, though as only 16 out of 158 babies had rooms to themselves at 3 months, the evidence here is rather tenuous. It was remarkable how easily those babies who slept in the living room would go to sleep with the whole family present making no special effort to be quiet.

These findings are in line with experimental evidence. Irwin and Weiss (1934) found that

continuous fairly strong stimuli—visual, auditory or cutaneous—are inhibitory in effect, at least on the newborn infant. We should not therefore expect the period of initial adjustment to be affected by a light room or noisy surroundings or by having to share a bedroom, however undesirable on other grounds.

Change of cot or of sleeping room was experienced by 46 infants under 3 months of age, only two of whom reacted with increased night waking. Such changes in themselves seem to have little effect at this stage, whereas from the fourth month on they fairly frequently produce temporary disturbance.

Changes of routine sometimes have a dramatic effect, either settling or unsettling, on young infants. In at least three cases a period in hospital for mother and child seemed to settle a baby that had always been wakeful before. The following case is an example:

CASE 856 (boy). First child, professional parents sharing part of house, living in one cheerful room. Some asphyxia at birth. Child woke and was fed nightly until mother (with child) admitted to hospital at 3 months. Child slept alone in hospital, was not fed, and stopped waking in night. Slept through after return home until two days of minor ailment at 5½ months started sleep disturbance which lasted through the remainder of the year.

Improved sleeping at night was also noted in one baby (836) who was in hospital alone from 18 to 23 weeks for gastro-enteritis. Mother visited daily and no serious adverse effects of separation were noted. The child had been prone to wake, though not nightly, and this had been indulgently but inconsistently handled. After her time in hospital she slept regularly through the night.

One of several possible reasons for the improvement shown in these two cases could be the change to a different and more stable routine. The change may have effectively broken up a situation which was unsatisfactory for both mother and child.

Even a minor change of routine, such as shifting the bath time from morning to evening, proved helpful in settling some infants. In other cases a temporary change, for example a holiday away, appeared to upset a good sleeper. Generally, as with illnesses, such upsets pass easily during the first three months, but at later ages they can be the signal for a prolonged spell of waking.

Relation of Night Waking to Social-demographic Factors. The father's occupational class shows no relationship with age of settling. There is, however, a difference between classes, significant at the 6% level, in the tendency for babies to wake over the year as a whole, more waking occurring in the skilled manual class (III) than in any other. This difference is not easy to explain; if not accidental, it would suggest subcultural differences which have yet to be elucidated.

Neither the mother's education nor the mother's age shows any relationship to settling age or tendency to wake.

The child's position in the family shows a relationship with age of settling significant at the 5% level, and a similar but rather less significant relationship with waking scores for the year. The significant difference lies not, as might have been expected, between only children and others, but between first and second children on the one hand and all subsequent children on the other. The figures are as follows:

	Total No.	Not Settled at 13 Weeks	% Not Settled
1st children ..	56	22	39·3
2nd children ..	55	21	38·2
Subsequent ..	43	9	20·9

We can conclude that the experience of having had previous children counts for more in mothers than age or education.

Relation of Night Waking to Parental Handling. The age of weaning from the breast shows no relationship to settling age or tendency to wake in the first three months, breast- and bottle-fed babies falling into roughly equal proportions on both criteria. The actual weaning had a settling effect on sleep in at least a dozen cases. In no case did weaning from the breast before 3 months, however sudden, lead to increased waking (we are not here considering other effects of weaning).

Flexibility of feeding times ('demand' *v.* 'clock' feeding) shows no relationship, the three groups, classed as 'demand fed', 'clock fed', and 'latitude allowed', containing approximately equal proportions of settlers and non-settlers and of children with high and low waking scores. Certain children, however, benefited from reasonable adaptation of timing that had proved too rigid.

Feeding in the night when the child cries can be considered separately. Mothers were classified as (i) feeding always (62 cases), (ii) feeding sometimes or after other methods tried (64), (iii) never feeding (22). Only three of the unfed babies or about 13% failed to settle by 13 weeks, as against 32% of those fed regularly and 40% of the variable group. These differences are of only borderline significance ($P<0{\cdot}07$) but are confirmed by similar trends in each of three subsamples (Groups B, C and D). When we turn to tendency to wake in the

year as a whole, however, the groups that were consistently fed and unfed in their early months have evened out their scores, while the group that received variable handling contains a significantly higher proportion of chronically wakeful babies ($P<0{\cdot}01$).

While some of the wakefulness of group (ii) may be attributed directly to inconsistent handling, which gives a child no firm basis on which to establish a regular sleeping rhythm, there may, too, be an indirect effect in that rapid shifts from method to method can be one expression of maternal anxiety, which probably communicates itself to the child through stresses and tensions during nursing, or in other ways, thereby affecting his ability to relax and sleep soundly. It must, however, be considered only rational in the parents of a persistently wakeful child to try a variety of methods. It is very probable that some of the mothers who never fed at night because their babies slept well without it would have done so had they persistently awakened.

Other methods of handling night waking are used in many combinations with varying immediate effect, but it is worthy of note that in contrast with feeding no other method is used solely and consistently as the effective answer by more than a handful of mothers.

Perhaps our most interesting finding is one that emerged as a by-product. Differences between settlers and non-settlers had been sought, but not found, in total duration of feeds (time in mother's arms) and in actual sucking time. It then occurred to us to take the difference between these as a measure of the time given by the mother to the baby for contact and play, over and above what he needs for feeding. (Where a mother props up the bottle and leaves the infant to take a part or the whole feed on his own, this difference can have a negative sign.) This quantity, which we have called 'excess nursing time', estimated at the three-month interview, turns out to discriminate very significantly between babies who settled by 13 weeks and those who did not. Not only are the differences significant at the 1% level, but similar patterns are found in each of the three sampling groups, B, C and D.

Whereas the babies that received least nursing had the greatest tendency to wake, those that received a rather excessive amount were the next most wakeful group, while those that had between 10 and 20 minutes in addition to their feeding time settled best. It is true that examples of both extremes appear among good sleepers and bad; but apparently for most children an adequate amount of contact with mother is an important factor conducing to the establishment of the sleeping rhythm.

Efforts were made to extend this finding to certain aspects of the mother's methods and personality by using a variety of rating and other methods.

In general, these indices failed to discriminate reliably between infants who settled and those who did not. The ratings on the subgroup receiving extra visits mostly gave differences in the expected direction, *i.e.*, the settled babies had mothers who were judged, as a group, to be more positively accepting, more self-confident, less anxious and showed less negative feeling towards their children; but of all the ratings, only those of one observer on positive acceptance reached the 5% level of significance for the 45 cases. With improved techniques and larger numbers it is quite possible that more of these maternal traits would turn out to be significant for sleep. For example, though rigidity, as judged by answers to certain questions, gave no discrimination, there were cases of very persistent waking which could only be attributed to the obsessional rigidity of the mother, such as the following:

CASE 896 (boy). Second child of professional parents, living in cramped top flat, kept very tidy. Mother felt guilty about having been inconsistent with her first child, who proved difficult, and determined to 'stick' to a pattern of handling with the second. Accordingly, though fond of the baby in her own way, she refused to feed in the night, or even to pick him up, in case he got used to it; fed strictly to clock times, even waking the child when he had just fallen asleep after several hours' crying; gave up nursing at feeds because 'his hands get in the way'; and when asked if she played with him, replied, 'only if I have time. I'm afraid he has to wait on my convenience'. Child continued waking once or more nightly to 9 months.

The following shows a very different maternal attitude which is also consistent with delayed settling:

CASE 936 (boy). First child of professional parents from Mediterranean country. Living in two rooms, good condition, clean and cheerful. Normal birth, healthy child, feeding satisfactory, breast to 8 months. Fed on demand, intervals remaining highly irregular. Optimal nursing times at feeds. Much finger sucking at 3 months. Mother very fond of child, but over-anxious and cannot bear to let him out of her sight as she is afraid he will suffocate, so carries him about and talks to him constantly during the day. Child scarcely ever sleeps by day; total sleep at 3 months estimated at 11½ hours. Fed regularly on waking at night. Waking falls below nightly level for a few weeks at the normal third-month settling period, but reverts to nightly from 3 to 6 months, then somewhat less to end of the year.

Finally we present two cases which may give some idea of the complex interaction of the various factors we have discussed:

CASE 884 (boy). Second child, superior working class family, living in grandparents' flat, well furnished and well kept. Blue asphyxia at birth. Healthy child. Mother, aged 40, had insufficient milk; complementary feeding from start, weaned at 2 weeks. 'Lazy' feeder; would not finish bottle but wanted it early. Mother would have preferred to feed to the clock, but allowed latitude after 6 weeks. Much sucking of fingers and of dummy after initial refusal. Long nursing time at 6 weeks, none at 3 months because mother said child 'preferred' to take bottle on his own. Mother an anxious person with little natural aptitude for handling children. Inconsistent at night; usually ended by taking child into her bed until he ceased to respond to this method. Stopped night feeding about 6 weeks, though child responded regularly. Continued waking once nightly to 11½ months.

CASE 860 (boy). First child, working class family in poor tenement flat. Normal birth, healthy child. Fed well but started refusing breast occasionally and preferring bottle from 7 weeks on; this coincided with mother's resumption of part-time work, during which father cared for the child. Weaned at 8 weeks. Excess nursing time nil at 3 months. Mother fond of child but worried by serious friction with husband. Child cried much during first two nights at home, then nightly; weaning from breast made no difference, until solids were introduced at 20 weeks. Inconsistent handling at night.

General Discussion

Do babies 'learn' to sleep through the night? There is a philosophy which assumes that anything that can be learnt can, and should, be taught. As regards sleep, this places the full responsibility on the parents. 'A sleepless baby is a reproach to his guardians', wrote Sundell in 1922. This idea is still current, especially among mothers who rely on out-of-date advice from their own parents and others, and is readily embraced by those with a tendency to rigidity or to anxious self-reproach.

The truth appears to be that there is a natural tendency for infants to lengthen their period of continuous night sleep while curtailing that taken by day.

What we have called the 'settling' process, a form of learning at the level of biological adaptation, requires no consciously directed training by the parents. There are indications that it is connected with fundamental physiological changes affecting the whole pattern of mental and physical activity. Generally it takes its course, and if disturbed by illness or change, will be resumed when the disturbance is past. If it is delayed beyond the fourth or fifth month, however, this automatic gravitation to the diurnal cycle may be lost, and adjustment may then be very difficult to attain, perhaps because the organism has reached a point of stabilization on a different rhythm. Where such children sleep through after a spell in hospital or a holiday away, it may be that the radical change in daily routine, by breaking up this heterodox rhythm, has cleared the way for a final adjustment to the ordinary pattern.

More surprising than the number of deviants from the norm, when all is considered, is the number who adhere to it in the face of difficulties. Of all the adverse factors we have discussed, not one but applied to some children who slept through the night notwithstanding.

An examination of the factors associated with continued waking suggests that failure to settle may sometimes be due to lack of wisdom in the parents: if so, it seems quite likely to result from insufficient nursing by the mother, either on principle or for lack of time or lack of inclination; or, on the other hand, from excess of anxious, over-solicitous mothering; or from erratic behaviour springing either from fecklessness or from ambivalence to the child; or, in some cases, from a rigid, controlling attitude which seeks to impose an unsuitable régime. Equally, it would seem, the failure may have nothing to do with the parents, but may come from some cause within the child—delayed effects of asphyxia or other birth trauma, perhaps, or just constitutional sensitiveness, as in the baby who cries when handled. Sometimes there is a failure of adaptation on both sides, which can lead to a kind of war of attrition. Indeed, the interaction of these numerous factors is so complex that it is seldom possible to say definitely that a given child's failure to sleep is due to one particular cause.

Of the possible types of parental failure concerned, we wish to call particular attention to deficiency of nursing time. Its connexion with night waking appears to be established unequivocally, but the reasons for the connexion are not. What is the nature of the child's unsatisfied need? If it were merely for nursing as such, it would be difficult to explain why some children do sleep and thrive with a minimum of nursing. We suggest that the need is more probably for a certain basic quality of feeling in the mother, which finds expression in a number of ways, usually but not invariably including adequate nursing.

Where a child is nursed very little because the mother believes it is too restless to feed steadily in her arms, we have to ask, (*a*) Is it a physiological restlessness (*cf.*, Case 884)? (*b*) Has the child's interest in nursing been lost, or never developed, for lack of mutual enjoyment? (*c*) Or is it, as with some babies whose mothers complain that 'he only wants to play', that what is really a desire to play and

communicate with mother between sucks is misinterpreted as unwarrantable dalliance and lack of interest in food?

Making full allowance for domestic and other commitments, it still appears probable that the mother who takes very little or no time for cuddling and fondling her baby is failing to follow the normal maternal instinct.

The better sleeping record of third and subsequent children is of interest in this connexion. Their mothers, as a group, may be presumed to be more practised in handling babies, less anxious about minor disturbances, and less emotionally involved with the individual child than the mothers of only one or two; also busier, but probably more maternal, and thus in general likely to mother their babies in a warm, competent and healthily balanced way.

It remains true, however, that some mothers give insufficient time to nursing on principle, thinking it best not to 'spoil' the child, or acting on advice. Where advice is to be given, our findings suggest that a moderately generous amount of nursing and play is to be recommended from the earliest months, as conducing to sound sleep as well as to happy relationships.

Finally, we have to remember that sleep is by no means an invariable sign of good health nor of good adjustment. Indeed, many children suffering from faulty adjustments of various kinds seem to sleep particularly soundly, as though recovering energy expended in crying or otherwise combating their difficulties. On the other hand, in a well and happy infant, even nightly waking need not be regarded as too serious a problem, provided the parents can accept it without resentment, self-reproach or other ill-feeling, deal with it efficiently and get enough sleep. Prolonged spells of waking more than once in the night are, of course, likely to indicate some faulty adjustment in the child or family calling for a thorough review of the whole situation with professional advice.

Summary

Of 160 infants whose mothers were seen at intervals from birth, about 70% had ceased night waking (between midnight and 5 a.m.) by the age of 3 months, and 83% by 6 months. Ten per cent. never started sleeping regularly through the night for as long as four weeks during the first year.

Of those who settled, about one-half had subsequent spells of night waking of more than four weeks' duration. The majority of these fresh disturbances had their onset between the ages of 5 and 9 months. A tendency to night waking was found to be associated with neonatal asphyxia, deficiency of nursing time and a number of other factors. Possible causes are discussed.

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References

Aserinsky, E. and Kleitman, N. (1955). *J. appl. Physiol.*, 8, 11.
Bühler, C. (1930). *The First Year of Life*. New York.
Darke, R. A. (1944). *J. Pediat.*, **24**, 148.
Despert, J. L. (1949). *Nerv. Child.*, **8**, 8.
Erwin, D. (1934). *J. genet. Psychol.*, **45**, 199.
Gesell, A. and Ilg, F. L. (1937). *Feeding Behaviour of Infants*. Philadelphia.
Griffiths, R. (1954). *The Abilities of Babies*. London.
Hellström, B. and Jonsson, B. (1953). *Acta paediat.* (*Uppsala*), **42**, 398.
Illingworth, R. S. (1951). *Brit. med. J.*, **1**, 722.
—— (1953). *The Normal Child*. London.
Irwin, O. C. and Weiss, LaB. A. (1934). *Univ. Iowa Stud. in Child Welfare*, **9**, No. 4, Pt. 5, p. 163.
Kleitman, N. (1939). *Sleep and Wakefulness*. Chicago.
—— and Engelmann, T. G. (1953). *J. appl. Physiol.*, **6**, 269.
Lewin, B. D. (1951). *The Psychoanalysis of Elation*. London.
Marquis, D. P. (1941). *J. exp. Psychol.*, **29**, 263.
McNemar, Q. (1949). *Psychological Statistics*. New York.
Moore, T., Hindley, C. B. and Falkner, F. (1954). *Brit. med. J.*, **2**, 1132.
Preston, M. I. (1945). *J. Pediat.*, **26**, 353.
Ribble, M. (1943). *The Rights of Infants*. New York.
Rosenfeld, G. B. and Bradley, C. (1948). *Pediatrics*, **2**, 74.
Shepherd, F. (1948). *Disturbed Sleep in Infancy and Childhood*. Hatfield, England.
Sperling, M. (1949). *Nerv. Child*, **8**, 28.
Sundell, C. E. (1922). *Practitioner*, **109**, 89.
Thompson, H. (1936). *Psychol. Monogr.*, **47**, No. 2, p. 64.
Walter, W. Grey (1956). *Electroencephalographic Development of Children*. In Tanner, J. M. and Inhelder, B. (ed.) *Discussions on Child Development*, Vol. I, p. 132.
Wagner, I. F. (1937). *J. genet. Psychol.*, **51**, 17.
—— (1939). *Ibid.*, **55**, 121.

A PRELIMINARY REPORT ON THE PATHOLOGY OF THE PITUITARY GLAND IN CHILDREN WITH MALNUTRITION

BY

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There have been a number of reports on the general pathology of malnutrition, especially kwashiorkor, which have included careful studies of the exocrine glands (Davies, 1948; Jelliffe, Bras and Stuart, 1954; Tejada, 1955). However, little is known of the pathology of the endocrine glands in this condition. Clinical studies of malnourished adults show that they may have pigmentation of the skin, lowered metabolic rates, gynecomastia, asthenia and sexual disturbances (Jacobs, 1948; Klatskin, Salter and Humm, 1947; Zubirán and Gómez-Mont, 1953; Zubirán, Gómez-Mont and Laguna, 1955). Furthermore, there may be severe depletion of protein enzymes (Scrimshaw, Béhar, Pérez and Viteri, 1955; Véhelyi, 1948). Because of these facts, some authors have postulated that pituitary hypofunction comparable to 'panhypopituitarism' is characteristic of extreme malnutrition (González Valero, Garcia Reyes and Gómez-Mont, 1950; Paullada, 1955; Zubirán and Gómez-Mont, 1953; Zubirán *et al.*, 1955). Pathological studies of the pituitary itself, however, are rare, and consist of observations on adults suffering from general malnutrition (Paullada, 1955, Zubirán and Gómez-Mont, 1953) or anorexia nervosa (Richardson, 1939; Siebenmann, 1955; Wilson, 1954). The purpose of this paper is to report the pathological anatomy of the pituitary in children with malnutrition.

Material

Nineteen children dying in the General Hospital of Guatemala were studied. Clinical data are summarized in Table 1. The children were classified in three groups, according to nutritional characteristics as previously described (Jelliffe, 1955; Scrimshaw, Béhar, Arroyave, Viteri and Tejada, 1956).

(1) **Kwashiorkor (Nine Cases).** This is a syndrome of severe malnutrition, characterized by growth retardation, apathy, anorexia, oedema, pellagroid dermatosis, changes in the character and colour of the hair and muscular wasting. Autret and Behar (1954) have reviewed this syndrome in Central America, where it is named 'Síndrome pluricarencial de la infancia', and shown it to be identical in its major aspects with kwashiorkor as described elsewhere.

(2) **Pre-kwashiorkor (Síndrome de Pluricarencia Incipiente) (Four Cases).** This is a state of chronic malnutrition which is quickly followed by frank kwashiorkor after an episode of stress such as may result from infectious diarrhoea. The child shows retardation in growth and bone maturation. The hair is dull and brittle. The skin is usually dry and shows fine desquamation. Psychic changes such as moderate anorexia, apathy or irritability are usually present. In some cases there is also mild oedema.

(3) **Marasmus (Six Cases).** Marasmus is a state of infantile starvation, characterized by marked underweight, with atrophy of both muscles and subcutaneous fat. The face is monkey-like, due to the absence of fat pads in the cheeks. Neither hair and skin changes nor oedema are ordinarily observed.

Kwashiorkor and mild kwashiorkor are due primarily to a lack of protein in the diet; caloric intake may be adequate or somewhat diminished. Marasmus, on the other hand, is due primarily to a grossly inadequate caloric intake. As combinations of these two conditions may exist, a sharp division of cases is difficult to make. In fact, the element of marasmus is so common in the Central American form of the disease that it is often called marasmic kwashiorkor.

Methods

A complete necropsy was performed. The immediate cause of death for each case is listed in Table 1. Special attention was paid to the endocrine glands. The adrenals, thyroid and pancreas were carefully dissected and weighed immediately on a laboratory balance. These organs and the gonads were sectioned and stained with haematoxylin and eosin.

The pituitary glands were weighed on a torsion balance after fixation in formol-sublimate and serially sectioned in the horizontal plane. A differential count was performed on three sections of each gland stained by

TABLE 1
CLINICAL DATA ON 19 MALNOURISHED CHILDREN

Necropsy No.	Sex	Age	Weight (kg.)	Height (cm.)	Days in Hospital	Cause of Death
	Marasmus					
258	M.	13 mth.	4·99	65	2	Bronchopneumonia
249	M.	2 yr.	4·99	65	3	Bronchopneumonia
273	M.	3 yr.	6·98	85	19 hours	Bronchopneumonia
350	M.	4 yr.	6·08	80	8	Acute infectious colitis Bronchopneumonia
268	M.	8 yr.	9·02	93	3	Acute infectious colitis Bronchopneumonia
253	M.	1 yr.	5·90	67	6	Acute infectious colitis Lobar pneumonia
	Pre-kwashiorkor					
244	M.	16 mth.	9·07	70	1	Bronchopneumonia
293	M.	18 mth.	5·31	68	13	Bronchopneumonia
295	M.	4 yr.	9·07	88	4	Bronchopneumonia
251	F.	9 mth.	6·35	55	4	Acute infectious colitis Bronchopneumonia
	Kwashiorkor					
282	M.	15 mth.	5·40	70	6	Bronchopneumonia
331	M.	18 mth.	6·48	70	16	Bronchopneumonia
325	M.	3 yr.	7·66	84	15	Bronchopneumonia with abscess formation
298	M.	5 yr.	8·89	90	12	Bronchopneumonia
281	F.	15 mth.	6·71	74	12	Bronchopneumonia
307	F.	2 yr.	6·12	70	2	Bronchopneumonia
322	F.	3½ yr.	5·90	77	4	Pyelonephritis
278	F.	4 yr.	6·71	74	4	Unknown
292	F.	5 yr.	12·70	85	2	Bronchopneumonia

periodic-acid-Schiff-orange G, one through the centre of the gland, one some distance above, and one below the first cut. All the cells in every third oil-immersion field were examined.

The following cell types were classified:

(1) **Normal Basophils.** These were round or ovoid, intensely Schiff positive, densely granular cells which occur chiefly around the periphery of the anterior lobe in a normal hypophysis.

(2) **Amphophils.** Amphophils are round or polygonal cells which are frequently larger than the normal basophils and tend to have indistinct cell boundaries. They contain sparser and more weakly Schiff-positive granules, which are often irregularly distributed and may vary in size.

(3) **Hypertrophic Amphophils.** These cells are characterized by giant nuclei which may be of irregular shape and frequently contain a prominent nucleolus. They are derived from the sparsely granulated Schiff-positive cells through enlargement of the nucleus and degranulation of the cytoplasm.

(4) **Acidophils.** These are rounded, densely granular cells which are most abundant in the postero-lateral portions of the anterior lobe. The granules are Schiff-negative but stain with orange G.

(5) **Chromophobes.** These are apparently agranular cells which are usually much smaller than the cell types previously described. They are differentiated from the agranular hypertrophic amphophils by the size of the nucleus.

Results

The findings in the pituitary gland are shown in Table 2. The pituitary weight averaged 108 mg. in the children with marasmus, 138 mg. in pre-kwashiorkor and 154 mg. in frank kwashiorkor. It ranged from 60 mg. in a 13-month-old boy with marasmus to 210 mg. in a 45-month-old girl with kwashiorkor. No gross abnormality was found in any patient.

Normal basophils averaged approximately 8% in children with marasmus or pre-kwashiorkor, 11% in those with kwashiorkor. They ranged from 3·7 to 16·8% of the total differential count. Acidophils averaged approximately 14% in children with marasmus or kwashiorkor, 16% in those with pre-kwashiorkor. They were extremely variable, ranging from 1·7% to 33·8% of the total count. Chromophobes comprised the bulk of the cell population, averaging from 65 to 70% of the count.

The sparsely granulated amphophils, which previous studies have suggested may be the functionally active cells in the hypophysis (Russfield, 1957), were present in all cases, averaging about 8% in children with marasmus or kwashiorkor, and 5% in children with pre-kwashiorkor. They tended to be most numerous in children with very low percentages of well-granulated acidophils. In one gland from a patient with kwashiorkor (Case No. 325) in which only 1·7% acidophils were found, the amphophils were sufficiently numerous as to suggest adenomatous hyperplasia, and mitotic figures were present. The

TABLE 2
DIFFERENTIAL COUNTS ON PITUITARIES OF MALNOURISHED CHILDREN

Necropsy No.	Pituitary Weight (mg.)	Total Cells Counted	NB %	Ac %	Chr %	Amp %	HA %
	Marasmus						
258	60	6,123	3·7	26·0	63·6	5·1	1·6
249	80	4,883	5·1	5·2	86·7	2·6	0·4
273	160	7,077	11·3	2·4	69·4	14·6	2·3
350	70	7,145	14·3	17·8	57·5	9·2	1·2
268	150	5,650	9·9	5·5	73·9	9·8	0·9
253	125	4,093	4·8	26·2	63·8	3·9	1·3
Average	108		8·2	13·9	69·1	7·5	1·3
	Pre-kwashiorkor						
244	110	4,342	12·2	14·6	64·5	7·8	0·9
293	150	5,560	8·2	10·1	76·1	5·1	0·5
295	180	7,545	8·3	16·8	71·8	2·2	0·9
251	110	5,581	4·8	23·4	67·0	4·2	0·6
Average	138		8·4	16·2	69·9	4·8	0·7
	Kwashiorkor						
282	150	5,676	9·3	10·6	68·3	10·3	1·5
331	80	8,484	11·8	3·0	72·5	10·8	1·9
325	130	7,644	11·1	1·7	68·6	15·6*	3·0
298	180	7,327	9·1	15·9	63·9	9·9	1·2
281	100	5,951	9·5	18·8	64·5	4·4	2·8
307	200	7,335	11·2	10·1	74·5	2·3	1·9
322	150	5,645	7·8	10·2	70·1	10·8	1·1
278	210	7,560	10·6	17·3	64·8	6·1	1·2
292	190	6,819	16·8	33·8	40·7	7·5	1·2
Average	154		10·8	13·5	65·4	8·6	1·7

* Mitotic figures.
NB=normal basophils; Ac=acidophils; Chr=chromophobes; Amp=amphophils; HA=hypertrophic amphophils.

hypertrophic amphophils which are characteristic of every active pituitary (Mellgren, 1945; Russfield, 1957) were also present in all cases, averaging 1·3% in patients with marasmus, 0·7% in pre-kwashiorkor and 1·7% in marasmus. The range was 0·4 to 3·0%.

Because of the inherent variability of the material and the few cases available, the small differences observed among the various groups are not felt to be significant.

In all cases, the thyroid contained follicles of varying sizes. Seven glands contained colloid and 12 did not. The epithelium was usually cuboidal, although in two patients it was columnar. The testes showed only minimal signs of maturation, as would be expected in normal children of this age group. In three ovaries, however, developing follicles were present. The adrenals tended to be small. In eight cases the cortex had a linear pattern, the nuclei were pyknotic and abundant lipoid was present in coarse droplets. In 11 cases, the nuclei were large and vesicular, there were varying degrees of lipoid exhaustion, and the linear cortical pattern was obscured, although no frank nodularity was seen. The thymus was so small it was often difficult to find grossly. Microscopically it showed atrophy in all cases. Islets of Langerhans were abundant in all patients and appeared hyperplastic in nine.

Although no exact correlation between the differential counts in the pituitary and the histology of the end organs was apparent on preliminary survey, further studies are being carried out.

Discussion

Unfortunately, no necropsies on well-nourished Guatemalan children were available for comparison. The average numbers of basophils in the pituitaries described here were within the normal limits reported by Rasmussen (1950) for well-nourished children in the United States. Acidophils were usually, but not always, decreased. By the criteria of Mellgren (1945), who studied the pituitaries of Scandinavian infants, amphophils and hypertrophic amphophils were often significantly increased.

Previously descriptions of the adult human pituitary in malnutrition have varied widely. In patients dying of anorexia nervosa, both abundant normally granulated basophils and acidophils (Siebenmann, 1955) and decreased degranulated acidophils (Richardson, 1939; Wilson, 1954) have been reported. In one adult female with markedly decreased acidophils, there was hyperplasia of sparsely granulated cells staining with orange G (Wilson, 1954). Zubirán and Gómez-Mont (1953) have studied the pituitaries of 101 adults dying with chronic malnutrition. They report 'evidence of

atrophy' or 'degenerative lesions' in a high proportion of these, but no differential counts were performed. Paullada (1955), on the other hand, found no morphological alterations in the pituitaries of 30 undernourished adults. It is difficult to compare these reports with our findings because of differences in histological techniques and cell classifications used.

In adult pituitaries stained with P.A.S.-orange G, a hyperplasia of amphophils and a variable decrease in well granulated acidophils has been found to be characteristic of primary deficiency of the adrenals, thyroid or gonads, for which reason it has been postulated that the amphophils are the source of the trophic hormones in man (Russfield, 1957). It has also been found that an increase in the number of sparsely granulated Schiff-positive cells ('intermediate mucoid cells' or amphophils) relative to the number of fully granulated Schiff-positive cells ('maximal mucoid cells' or normal basophils) is the characteristic response of the human pituitary to stress (Currie and Symington, 1955).

The presence of unusually abundant amphophils in malnourished children would, therefore, suggest the production of trophic hormones in response to stress, although it is not possible to be sure of this point without biological analysis. The lipoid depletion seen in many of the adrenals and the striking thymic atrophy in all our patients may well be indirect evidence of A.C.T.H. production. To some extent, these findings resemble those of Siebenmann (1955) in anorexia nervosa and of Uehlinger (1955) in malnourished inmates of concentration camps. We would, therefore, agree with those previous workers who feel that there is no primary pituitary deficiency in malnutrition and that there may, indeed, be some evidence for overproduction of adrenocorticotrophic hormones.

Further studies are being carried out to clarify the role of the pituitary in relation to the other target organs.

Summary

The pituitary glands of 19 Guatemalan children with malnutrition (kwashiorkor, pre-kwashiorkor and marasmus) were studied histopathologically, differential cell counts being performed. Relative percentages of basophils were usually within normal limits established by others. Acidophils were inconstantly decreased. Sparsely granulated amphophilic cells, thought to be the source of trophic hormones, were often unusually abundant. It was concluded that no morphological evidence for panhypopituitarism had been found.

References

Autret, M. and Behar, M. (1954). Síndrome policarencial infantil (Kwashiorkor) and its prevention in Central America (Food and Agriculture Organization of the United Nations), *FAO Nutritional Studies*, No. 13, Rome.
Currie, A. R. and Symington, T. (1955). In *The Human Adrenal Cortex, Ciba Foundation Colloquia on Endocrinology*, **8**, 396.
Davies, J. N. P. (1948). *Lancet*, **1**, 317.
González Valero, E., García Reyes, J. and Gómez Mont, F. (1950). *Rev. Invest. clín.* **2**, 179.
Jacobs, E. C. (1948). *J. clin. Endocr.*, **8**, 227.
Jelliffe, D. B. (1955). *Infant Nutrition in the Subtropics and Tropics.* WHO Monogr. Ser. No. 29, Geneva.
——, Bras, G. and Stuart, K. L. (1954). *W. Indian med. J.*, **3**, 43.
Klatskin, G., Salter, W. T. and Humm, F. D. (1947). *Amer. J. med. Sci.*, **213**, 19.
Mellgren, J. (1945). *Acta path. microbiol. scand.*, Suppl. 60.
Paullada, J. J. (1955). *Rev. Invest. clín.*, **7**, 29.
Rasmussen, A. T. (1950). *Amer. J. Anat.*, **86**, 75.
Richardson, H. B. (1939). *Arch. intern. Med.*, **63**, 1.
Russfield, A. B. (1957). *The Endocrine System: The Adenohypophisis.* In *Analytical Pathology*, pp. 293-360, ed. R. C. Mellors, New York.
Scrimshaw, N. S., Behar, M., Pérez, C. and Viteri, F. (1955). *Pediatrics*, **16**, 378.
——, ——, Arroyave, G., Viteri, F. and Tejada, C. (1956). *Fed. Proc.*, **15**, 977.
Siebenmann, R. E. (1955). *Schweiz. med. Wschr.*, **85**, 530.
Tejada, C. (1955). *Rev. Col. Méd. Guatemala*, **6**, 1.
Uehlinger, E. (1955). In *The Human Adrenal Cortex, Ciba Foundation Colloquia on Endocrinology*, **8**, 92.
Véghelyi, P. V. (1948). *Acta paediat. (Uppsala)*, **36**, 483.
Wilson, R. R. (1954). *J. clin. Path.*, **7**, 131.
Zubirán, S. and Gómez-Mont, F. (1953). In *Vitam. and Horm.*, **11**, 97.
——, —— and Laguna, J. (1955). *Ann. intern. Med.*, **42**, 1259.

PULMONARY FUNCTION STUDIES IN NORMAL BOYS

BY

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That wheezy asthmatic children are unable to aerate their lungs as effectively as normal children has long been recognized, and it is generally believed that the severity of the 'asthma' is closely related to disturbance of the bellows function of the lungs. We have found subjective questioning and clinical examinations to be inadequate and often misleading for the assessment of asthmatic children. Consequently simple pulmonary function studies have been made as a routine on children attending an asthma clinic to provide a quantitative measure of disability, and to study more precisely the natural history of the various disease processes that give rise to asthma and difficulty in breathing. Such measurements are also useful in assessing quantitatively various forms of therapy, and help in differentiating reversible from irreversible lung changes.

Stewart (1922), Wilson and Edwards (1921), Moore and Gibson-Williams (1951) and others have shown that the pulmonary function of normal children varies with age and anthropometric build. However, the normal values of pulmonary function are dependent not only on the population studied but on the method of assessment and the apparatus used. At present it seems necessary for each group of workers to establish their own normal values (Wright, 1946). Therefore in this paper we report the results of pulmonary function studies and anthropometric measurements of 175 normal schoolboys between the ages of 8 and 14 years. We made this study in 1949 to provide the range of values that occur in normal schoolboys and to enable us to predict normal values for children of known age and stature.

Selection of Normal Children

The school from which the children were drawn was a state school in the Stoke-on-Trent area. The majority of the fathers were employed in the pottery and coal-mining industries. A nominal roll of all boys, listed according to age, was supplied by the school authorities, and from this list 175 children were chosen by random selection, in such a way as to give an unbiased sample of 25 children in each age group to cover each year of life between 8 and 14 inclusive. This random selection also provided two 'extras' for each age group should any child be found abnormal on clinical examination. Any child with clinical evidence of abnormalities of the respiratory system was excluded from the investigation.

Methods

Pulmonary Function Studies. The indices of ventilatory function that are listed below, together with their definitions, were carried out on each of the 175 normal children. All indices were measured in the sitting position with a nose clip. All values were corrected to 37° C. and saturated with water vapour.

Vital Capacity (V.C.). This is the maximum volume of air that can be expelled after a full inspiration. In this report the V.C. is taken as the mean of four readings as recommended by Gilson and Hugh-Jones (1949) and expressed in millilitres.

Vital Spirogram (V.S.). This is the tracing of the vital capacity, or full expiration, followed by full inspiration (Kennedy, 1953a). The expiratory phase is termed the expiratory vital spirogram (E.V.S.) and the inspiratory phase the inspiratory vital spirogram (I.V.S.).

The Expiratory Flow Rate (E.F.R.^{40}). This is half the expiratory flow rate during the first 0·75 second of the E.V.S. and is measured by means of a transparent protractor (Kennedy, 1953b). It is termed E.F.R.^{40}, since an expiratory time interval of 0·75 sec. is equivalent to a theoretical breathing rate of 40 breaths per minute. The E.F.R.^{40} is taken as the mean of four readings and expressed in litres per minute.

The Inspiratory Flow Rate (I.F.R.^{40}). This may be defined as above, but the inspiratory curve of the vital spirogram (I.V.S.) is measured instead of the E.V.S.

Maximum Voluntary Ventilation (M.V.V.) (Maximum Breathing Capacity or M.B.C.). This index was first described by Hermannsen (1933) and is defined as the maximum volume of air that can be shifted in unit time by voluntary hyperventilation. In this investigation each boy was asked to breathe in and out of a spirometer as deeply and as quickly as possible and the volume of air shifted was recorded on a kymograph. The mean of three six-second runs was taken as the M.V.V. and expressed in litres per minute.

Two Spirometers. The measures were obtained using two spirometers. A spirometer similar to that described by Gilson and Hugh-Jones (1949) was used for the various pulmonary function studies of boys between the ages 11 and 14 inclusive (Spirometer A). The shell of a Kendrick B.M.R. apparatus was modified to provide a smaller spirometer (Spirometer B) for the measurements on the younger boys aged 8-10 inclusive.

The kymographs used with spirometers A and B had drum periphery speeds of 1·24 cm./sec. and 1·0 cm./sec. respectively.

Anthropometric Measurements. The following anthropometric measurements were made with the child in socks stripped to the waist: The weight in lb., the height, the stem height and the chest measurements at the level of the nipples were made to the nearest quarter inch.

Results

Fig. 1 shows a vital spirogram typical of that found in a normal child of 11½ years. It will be seen that the expiratory phase is linear and uniform except during the expulsion of the last small volume of air, whilst the inspiratory phase is linear throughout its whole length. From a glance at the spirogram it can be seen what fraction of the vital capacity is the most efficient for hyperventilation. In this typical example taken from a normal healthy boy, it is apparent that all parts of the vital capacity, except for the last part of expiration, can be inhaled and expelled with almost equal efficiency.

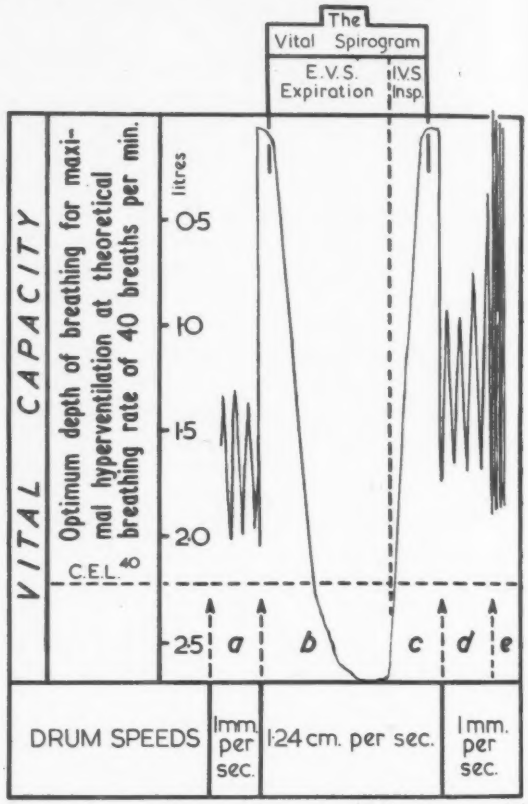

FIG. 1.—This continuous spirometric record of a normal boy aged 11½ shows:

(*a*) Quiet breathing at rest; (*b*) expiratory vital spirogram (E.V.S.); (*c*) inspiratory vital spirogram (I.V.S.); (*d*) quiet breathing + CO_2; (*e*) M.V.V. tracing at 65 breaths per minute.

R.R.L. = Resting respiratory level.

C.E.L.40 = Critical expiratory level at theoretical breathing rate of 40 breaths per minute.

TABLE 1

ANTHROPOMETRIC AND SPIROMETRIC MEASUREMENTS IN 175 NORMAL BOYS

No. of Boys in Each Group	Mean Age (yr.)	Mean Wt. (lb.)	Mean Ht. (in.)	Mean Stem Ht. (in.)	Mean Chest Circumference (in.)			V.C. (ml.)	M.V.V. (l./min.)	E.F.R.40 (l./min.)	I.F.R.40 (l./min.)
					Inspiration	Expiration					
25	8+5 mth.	58	50	28	26	24	Spirometer A	1688	55	57	42
25	9+6 mth.	65	52	29	27	24		1785	66	58	48
25	10+5 mth.	67	54	30	27	24		1975	71	65	54
25	11+7 mth.	74	55	30	28	25	Spirometer B	2083	71	71	70
	(3 mth.)	(13)	(2)	(1)	(2)	(2)		(245)	(12)	(10)	(15)
25	12+4 mth.	77	56	31	28	26		2158	76	77	73
	(3 mth.)	(9)	(3)	(1)	(1)	(1)		(368)	(14)	(13)	(15)
25	13+6 mth.	90	59	32	30	27		2405	76	83	72
	(3 mth.)	(14)	(4)	(2)	(2)	(2)		(508)	(14)	(14)	(14)
25	14+5 mth.	104	62	34	31	28		2986	99	103	100
	(3 mth.)	(12)	(2)	(2)	(1)	(1)		(450)	(16)	(14)	(19)

Spirometric Measurements at Different Age Groups. The average values of the anthropometric and spirometric measurements of the 25 boys in each of the different age groups are given in Table 1.

The vital capacity values rise fairly uniformly by between 75 ml. and 247 ml. with each extra year of life up to 13 years of age. Between 13 and 14 the vital capacity increases by more than 500 ml. as shown graphically in Fig. 2. The results suggest that the type of spirometer has had very little effect on the vital capacity readings.

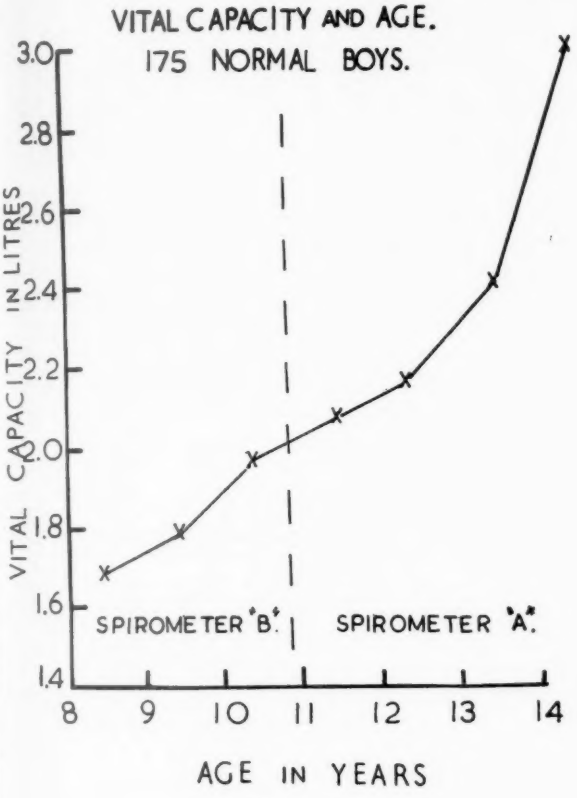

FIG. 2.

The mean values of the M.V.V. and E.F.R.^{40} and I.F.R.^{40} for each age group are plotted in Fig. 3. Theoretically, one would expect the M.V.V. curve to lie between the E.F.R.^{40} and the I.F.R.^{40} curves. However, with spirometer B, the mean M.V.V. values of the 9- and the 10-year-olds are higher than the corresponding E.F.R.^{40} and I.F.R.^{40} values. This anomoly is almost certainly instrumental and may be explained by the fact that the oscillation of the water column was considerably greater in spirometer B than in spirometer A during the performance of the M.V.V. test. This effect of a 'swinging' water column in enhancing M.V.V. values at different rates of breathing has been fully investigated by Bernstein, D' Silva and Mendel (1952).

The mean values of the M.V.V., E.F.R.^{40} and I.F.R.^{40} of the children measured with spirometer A closely approximate to one another and they all show the greatest yearly increase in the 14-year-olds. The mean E.F.R.^{40} increases remarkably uniformly in the age groups 9 to 13 inclusive, suggesting that this index, unlike the M.V.V., is not unduly affected by the type of spirometer.

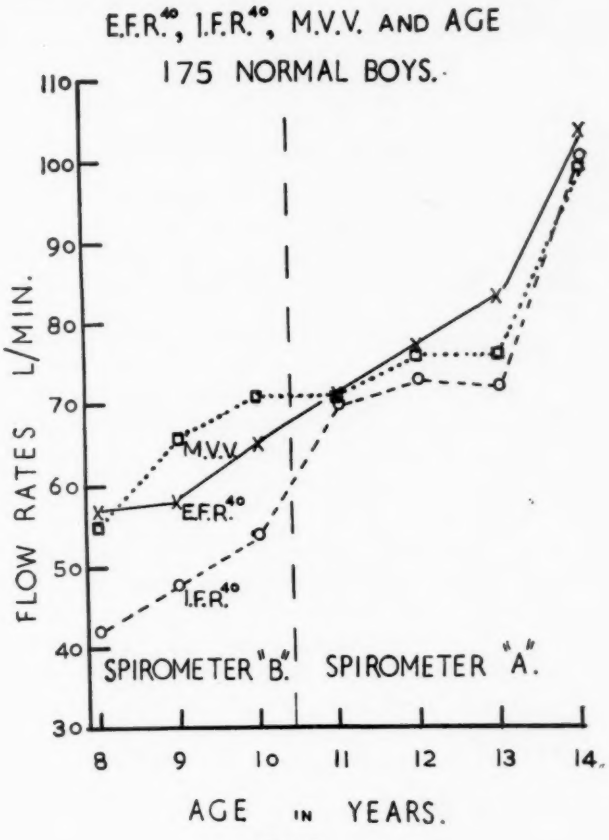

FIG. 3.

Interrelation of Spirometric and Anthropometric Measurements. The interrelation of the various indices is shown by the correlation coefficients which are listed in Table 2. These correlation coefficients relate to measurements made with spirometer A on 100 boys, as in all our later studies we have employed only this spirometer which is suitable for the assessment of both adults and children.

Of the anthropometric measures stem height shows the best correlation with the spirometric measures, followed by standing height and weight, whilst age and the various chest measurements show less

TABLE 2
CORRELATION COEFFICIENTS AT AGES 11 TO 14

	Height	Standing Height	Weight	P.A. Inspiration	P.A. Expiration	Circumference Inspiration	Circumference Expiration	Age	E.F.R.	I.F.R.	V.C.
Standing height	0·720	—	—	—	—	—	—	—	—	—	—
Weight ..	0·848	0·782	—	—	—	—	—	—	—	—	—
P.A. inspiration	0·575	0·673	0·695	—	—	—	—	—	—	—	—
P.A. expiration	0·511	0·474	0·673	0·897	—	—	—	—	—	—	—
Circumference inspiration	0·222	0·183	0·290	0·232	0·233	—	—	—	—	—	—
Circumference expiration	0·672	0·492	0·855	0·661	0·655	0·285	—	—	—	—	—
Age	0·676	0·692	0·676	0·430	0·447	0·193	0·584	—	—	—	—
E.F.R. ..	0·772	0·768	0·702	0·594	0·524	0·210	0·518	0·620	—	—	—
I.F.R. ..	0·507	0·588	0·468	0·428	0·352	0·143	0·326	0·418	0·786	—	—
V.C.	0·812	0·847	0·801	0·637	0·578	0·243	0·638	0·602	0·893	0·625	—
M.B.C. ..	0·627	0·711	0·639	0·497	0·449	0·184	0·485	0·519	0·637	0·936	0·705

correlation. Of the spirometric measures the V.C. shows the best correlation with stem height, standing height and weight followed by E.F.R.[40] and M.V.V. and with the I.F.R.[40] showing the lowest correlation. Within the four spirometric measures, the vital capacity correlates best with the E.F.R.[40] (r=0·893) whilst the M.V.V. correlates best with the I.F.R.[40] (r=0·936). For reasons which are discussed later we have employed the E.F.R.[40] as our measure of the bellows function of the lungs: we will now consider how we may predict normal values for boys of known age and build.

Estimation of Expected Normal E.F.R.[40] of a Boy. The three anthropometric measurements that correlate best with the E.F.R.[40] are standing height (r=0·772), stem height (r=0·786) and weight (r=0·702), whilst some of the chest measurements show a smaller but significant correlation. For the assessment of results in abnormal children it is necessary to be able to predict normal values—weight and chest measurements are usually more altered by disease processes than height—and we have therefore rejected the former measures for prediction purposes. We consider height and age to be the most relevant indices for calculating the expected normal E.F.R.[40], and employ the following regression equation.

$$E.F.R.^{40} = 3{\cdot}23 \times X_1 + 2{\cdot}41 \times X_2 - 135$$

where X_1 = height in inches
X_2 = age in years

For convenience in clinical work this regression equation has been translated into a nomogram (Fig. 4). If on the nomogram, the age and height of a subject be joined by a ruler, the predicted E.F.R.[40] is given by the point of intersection with the E.F.R.[40] scale.

Regression Equations for Prediction of V.C., M.V.V. and I.F.R.[40] in Boys Aged 11-14 Years. If for the reasons given previously one excludes weight and chest measurements for the prediction of normal values of the V.C., M.V.V., and I.F.R.[40], the best prediction formulae for the various indices on the basis of standing height are given below. The prediction of the indices listed below is not materially improved by allowing for age as well.

V.C. = $115{\cdot}93x_1 - 4348$ ml. (S.D. 290 ml.).
M.V.V. = $2{\cdot}98x_1 - 93{\cdot}4$ l./min. (S.D. 13·2 l./min.).
I.F.R.[40] = $3{\cdot}06x_1 - 97{\cdot}4$ l./min. (S.D. 15·7 l./min)..
where x_1 = standing height in inches.

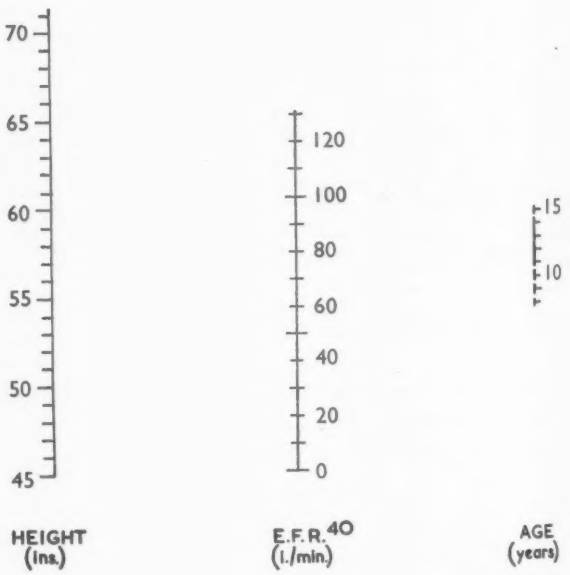

FIG. 4.

Discussion

The results of the various spirometric measures on the 175 normal school children presented in this paper were all obtained in a school room temporarily

set aside for the purpose. The four spirometric measures (V.C., M.V.V., E.F.R.[40] and I.F.R.[40]) of each individual boy that have been included in the analysis are the mean of four consecutive values. We think it important to stress these conditions under which the observations were made, and also the method of analysis, because we believe these factors may be responsible for our predicted and recorded values being slightly lower than those reported by some other authors.

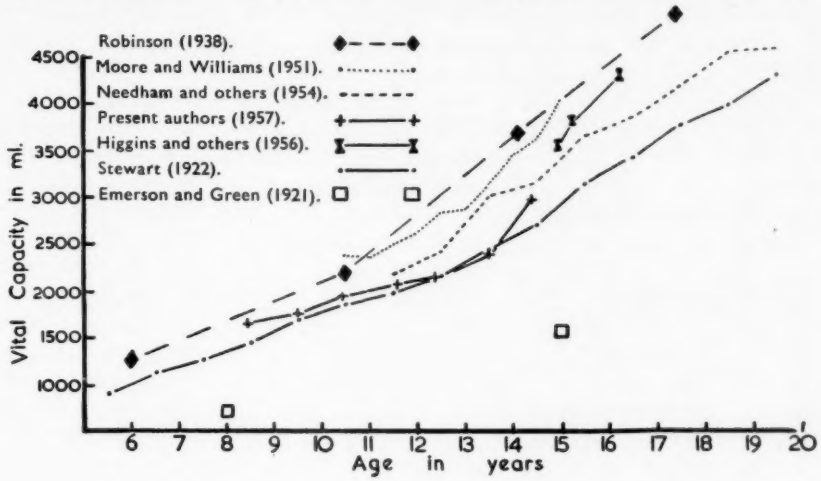

FIG. 6.

Absolute Values Compared with Those of Previous Workers. The different absolute values of the various spirometric measures reported here and by previous workers can largely be explained on the basis of three variables, namely, the physical characteristics of the children studied, the method and the procedure employed in obtaining the results.

Fig. 5 shows the standing height and age of the boys studied by us and of boys studied by previous workers with comparable data, whilst Fig. 6 gives the vital capacity plotted against age. If Figs. 5 and 6 be compared, it will be seen that the highest vital capacities at the different ages were reported by those workers (Robinson, 1938; Moore and Gibson-Williams, 1951) who studied taller boys than the other workers. The heights of the boys of different ages reported by us appear comparable with those studied by Stewart (1922), Needham, Rogan and McDonald (1954) and Higgins, Oldham, Merrick and Dunsdon (1956). Our V.C. values agree well with those of Stewart and also of Everley Jones (1955), who studied a group of Midland school children similar to our sample. The values obtained by Needham *et al.* for boys aged 11 to 14 inclusive are slightly higher than our values, possibly because they took the highest of four attempts as the V.C., whereas we took the mean of four attempts as recommended by Gilson and Hugh-Jones (1949). The low values reported by Emerson and Green (1921) cannot be explained on the basis of height, and it is possible that the big differences between these and other authors may be due to the apparatus used. Higgins *et al.* used a low-resistance spirometer almost identical to our adult spirometer and, allowing for the height differences, the V.C. value of their 14-year-olds seem compatible with our values. Most of the data in Fig. 6 show that the vital capacity, like the height, increases more during the years of puberty.

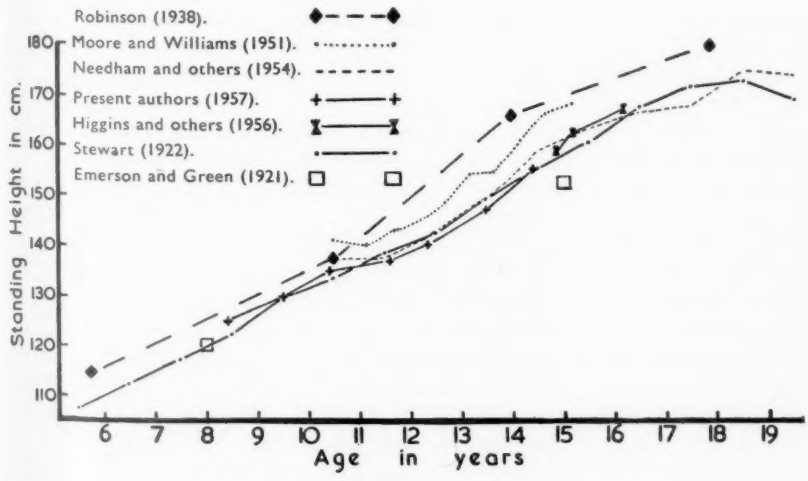

FIG. 5.

Morse, Schlutz and Cassels (1952), studied normal boys aged 11-17 years, and found that the vital capacity occupies roughly 80% of the total lung volume; this finding also holds true for normal young adults (Kaltreider, Fray and Hyde, 1938; Robinson, 1938). Thus, if one finds the vital capacity of an adolescent or a young adult to be as good or better

than the predicted normal value, then it would be reasonable to expect the other sub-divisions of the total lung volume to be within normal limits also.

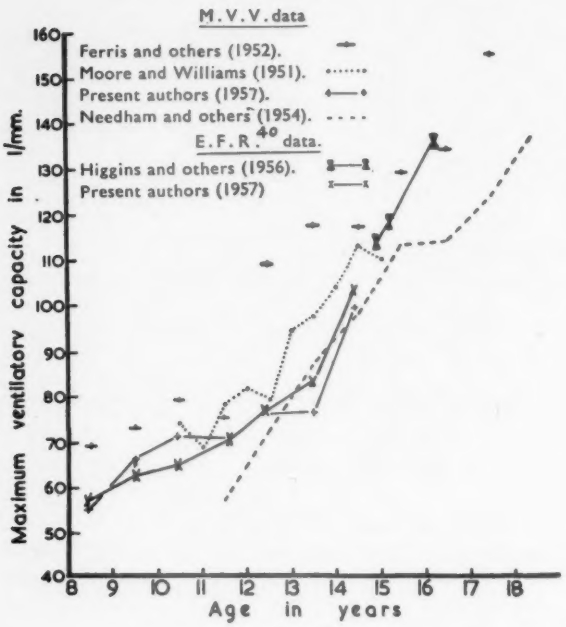

FIG. 7.

Except for our group aged 13 years, our M.V.V. and E.F.R.[40] curves in Fig. 7 run roughly half way between Moore and Williams' M.V.V. curve and that of Needham *et al.* Needham *et al.* used a Douglas bag to obtain their M.V.V. data, and the difficulty of ensuring full cooperation with this technique may be responsible for their lower values. Bernstein *et al.* (1952) have shown the effect of different rates of breathing on the M.V.V. and they also show the effects of oscillating water columns in various spirometers in enhancing M.V.V. values. Our experiences with spirometer A and spirometer B support their findings. The relatively higher values of Moore and Williams may be partly explained by the size of the children and possibly by the enhancing effect of water oscillation within their spirometer: The same arguments may possibly explain the even higher values obtained by Ferris, Whittenberger and Gallagher (1952). Our own E.F.R.[40] data and those of Higgins *et al.* appear compatible: this is perhaps not surprising, because unlike the M.V.V. test the E.F.R.[40] test is not susceptible to different breathing rates nor is it affected much by an oscillating water column. McDermott and McKerrow (1956) have also shown the E.F.R.[40] to be largely independent both of the resistance at the mouth-piece orifice and of the patient's cooperation provided a full inspiration is taken.

Prediction Formulae. Table 2 shows that age, height, weight and chest circumference are all correlated with the various spirometric measures. These findings would agree with the suggestion by Whitfield, Waterhouse and Arnott (1950) and that of Ferris *et al.* (1952) that a number of physical attributes, including body surface area, should be employed for the prediction of normal vital capacity and M.V.V. values. However, we are interested in the prediction of so-called normal values in abnormal children, and the use of such indices as weight and chest circumference would obviously be fallacious in those children emaciated from certain diseases and those with chest deformities. Whereas in adolescents age shows a positive correlation with spirometric measures, there is a negative correlation in adults (Hutchinson, 1846; Baldwin, Cournand and Richards, 1948; Gilson, Hugh-Jones, Oldham and Meade, 1955). Thus clearly, formulae for the prediction of normal values in children which incorporate age are not applicable to adults and *vice versa*. The position in regard to weight is more complicated, since although in general weight is positively correlated with spirometric measures in both children and adults, excessive weight or obesity is associated with a reduction of the normal vital capacity (Hutchinson, 1846) and in all probability with a reduction of other spirometric measures also. It would thus appear that either standing height or sitting height is the most important single index for the prediction of normal spirometric values.

Although some authors use surface area (Moore and Gibson-Williams, 1951; Ferris, *et al.*, 1952), we have followed the practice of others in using height as our main index for the prediction of the different spirometric measures. Hutchinson (1846) in his classic treatise on the vital capacity discussed various groups of normal young adults, and estimated that for every inch increment of height from 5 to 6 ft., 8 additional cu. in. air (131 c.cm.) at 60° F. (cf. our prediction formula for vital capacity) are given out by forced expiration. Baldwin *et al.* (1948) also use height as their main index for the prediction of normal vital capacity values although they use body surface area for the prediction of normal M.V.V. values. Everley Jones (1955) measured the vital capacity of boys and girls and plotted height, weight and surface area against vital capacity. He was able to corroborate the finding of Baldwin *et al.* that the most smoothly rising curve in each sex was that recording vital capacity against height. It should be emphasized that the various prediction formulae for the E.F.R.[40], I.F.R.[40], V.C. and M.V.V. given in this paper are only strictly applicable to boys aged 10-15 years.

However, for practical purposes they are probably near enough for boys aged 7-18 years, although the values at either end of this age range are on the low side. The prediction formulae are not applicable to children and adolescents outside the 7-18 years range.

The standard deviations of the distributions of normal values (for a given height and age) are quite large: 10·7 litres per minute, for example, for E.F.R.^{40}. It is important, therefore, to remember that deviations from the predicted value of 20 to 30% are not uncommon even in boys in whom no significant abnormality can be demonstrated. A deviation of this magnitude should be regarded as suspicious, but far from conclusive.

Although we have not studied girls, there seems to be good evidence that normal boys and girls of the same height have very similar vital capacities (Everley Jones, 1955) and M.V.V.s (Ferris *et al.*, 1952; Ferris and Smith, 1953). Consequently we employ the same formulae for the prediction of normal values in girls as we use for boys.

Baldwin *et al.* (1948) measured the vital capacity data on adults, and on comparing their findings with those of Kaltreider *et al.* (1938) and Robinson (1938), they found that values decreased with age to about the same degree in both sexes. However, in adult life females have a lower vital capacity and a lower maximum ventilatory capacity than men of similar height and surface area (Baldwin *et al.*, 1948). Consequently formulae for the prediction of normal values in adults must allow for this sex factor.

Indices of Maximum Ventilatory Capacity (M.V.C.). Since introduced by Hermannsen in 1933 the M.V.V. test, recorded by means of a spirometer or a Douglas bag, has until recently been generally accepted as the best index of maximum ventilatory capacity. This test is time-consuming to both patient and observer and even if the technical problems already mentioned are eliminated the test is not suitable for routine out-patient work or for the assessment of severely disabled patients. Although we agree with Bernstein and Kazantzis (1954) and Shephard (1955) that the M.V.V. is well correlated with I.F.R.^{40} in normals (R=0·986) we have rejected this I.F.R.^{40} as an index of M.V.C. on two counts. First, in patients with ventilatory insufficiency it will nearly always be found that expiration is the limiting factor to hyperventilation. Second, to obtain satisfactory inspiratory curves (I.V.S.) the patient must always give of his best, whereas satisfactory expiratory curves (E.V.S.) are largely independent of the patient's cooperation, providing a maximal inspiration has been taken first. For these reasons we employ the E.F.R.^{40} test as our measure of maximum ventilatory capacity. We propose to retain the term E.F.R.^{40} (expiratory flow rate at theoretical breathing rate of 40 breaths per minute), because it describes the test and because the values are expressed in litres per minute which is the correct index for assessing ventilatory reserve.

Although the lungs must be capable of effective diffusion and be supplied with an adequate pulmonary blood flow to function properly under varying conditions and stresses, it has become more apparent during recent years that many respiratory diseases are disabling because they diminish the effective ventilatory capacity of the lungs. This argument applies particularly to such diseases as acute and chronic bronchitis (Westlake, 1955), acute and chronic asthma (Beale, Fowler and Comroe, 1952; Kennedy and Thursby-Pelham, 1956), localized cysts and generalized emphysema (Baldwin, Harden, Green, Cournand and Richards, 1950; Gaensler, 1951) and also patients with generalized lung fibrosis (Gilson *et al.*, 1955).

During our longitudinal study of asthmatic children over the past six years, we have for the above reasons been particularly interested in assessing the maximum ventilatory capacity by means of the E.F.R.^{40} test. When this test is applied to any individual child, it can be seen immediately whether there is any qualitative abnormality of the E.V.S., and by expressing the E.F.R.^{40} as a percentage of the predicted value, an index of the relative normality of the maximum ventilatory capacity is readily obtained, always bearing in mind the considerable range observed even in normal children.

Summary

One hundred and seventy-five schoolboys were selected at random from a school in the Stoke-on-Trent area to provide an unbiased sample of 25 normal boys for each year of life between the ages of 8 and 14 inclusive.

The anthropometric findings of these boys, which included height, sitting height, weight and various chest measurements, are reported.

The spirometric measures of these boys, which included the vital capacity (V.C.), maximum voluntary ventilation (M.V.V.), inspiratory flow rate at a theoretical breathing rate of 40 breaths per minute (I.F.R.^{40}) and the expiratory flow rate at a theoretical breathing rate of 40 breaths per minute (E.F.R.^{40}), are also reported.

The intercorrelation of the various anthropometric and spirometric findings are discussed and regression equations for the prediction of normal

values of the spirometric measures on the basis of standing height and age are given.

It is considered that the maximum ventilatory capacity of children and adolescents is best obtained by means of the E.F.R.[40] test, and a simple nomogram is given to facilitate the prediction of normal values.

The expiratory vital spirogram which is obtained during the course of the E.F.R.[40] test is of considerable clinical value in the assessment of individual patients.

We should like to thank Dr. Vera Veitch, Deputy Principal School Medical Officer to the Education Committee, and Mr. G. L. Light, Headmaster of Moorland Road C.P. Junior School, Stoke-on-Trent, for their invaluable help in arranging this investigation. We are indebted to Mr. J. Booth, S.R.N., Mr. T. E. Bromley, S.R.N. and Mr. L. Drury for skilled technical assistance, and also to the Photographic Department, St. Bartholomew's Hospital, London, for the figures.

References

Baldwin, E. de F., Cournand, A. and Richards, D. W. (1948). *Medicine, (Baltimore)*, **27**, 243.
——, Harden, K. A., Greene, D. G., Cournand, A. and Richards, D. W. (1950), *Ibid.*, **29**, 169.
Beale, H. D., Fowler, W. S. and Comroe, J. H. (1952). *J. Allergy*, **23**, 1.
Bernstein, L., d' Silva, J. L. and Mendel, D. (1952). *Thorax*, **7**, 255.
—— and Kazantzis, G. (1954). *Ibid.*, **9**, 326.
Emerson, P. W. and Green, H. (1921). *Amer. J. Dis. Child.*, **22**, 202.
Ferris, B. G. and Smith, C. W. (1953). *Pediatrics*, **12**, 341.
——, Whittenberger, J. L. and Gallagher, J. R. (1952). *Ibid.*, **9**, 659.
Gaensler, E. A. (1951). *Amer. Rev. Tuberc.*, **64**, 256.
Gilson, J. C. and Hugh-Jones, P. (1949). *Clin. Sci.*, **7**, 185.
——, ——, Oldham, P. D. and Meade, F. (1955). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 290.
Hermannsen, J. (1933). *Z. ges. exp. Med.*, **90**, 130.
Higgins, I. T. T., Oldham, P. D., Merrick, A. J. and Dunsdon, M. I. (1956). *Brit. J. prev. soc. Med.*, **10**, 32.
Hutchinson, J. (1846). *Med.-chir. Trans.*, **29**, 169.
Jones, H. Everley (1955). *Archives of Disease in Childhood*, **30**, 445.
Kaltreider, N. L., Fray, W. W. and Hyde, H. van Z. (1938). *Amer. Rev. Tuberc.*, **37**, 662.
Kennedy, M. C. S. (1953a). *Thorax*, **8**, 73.
—— (1953b). *Proc. roy. Soc. Med.*, **46**, 539.
—— and Thursby-Pelham, D. C. (1956). *Brit. med. J.*, **1**, 1511.
McDermott, M. L. and McKerrow, C. B. (1956). 20th Int. Physiol. Congress, Brussels Abstracts of Communications, p. 628.
Morse, M., Schlutz, F. W. and Cassels, D. E. (1952). *J. clin. Invest.*, **31**, 380.
Moore, R. E. and Gibson-Williams, M. G. (1951). *Gt Ormond Str. J.*, **1**, No. 2, p. 137.
Needham, C. D., Rogan, M. C. and McDonald, I. (1954). *Thorax*, **9**, 313.
Robinson, S. (1938). *Arbeitsphysiologie*, **10**, 251.
Shephard, R. J. (1955). *Thorax*, **10**, 258.
Stewart, C. A. (1922). *Amer. J. Dis. Child.*, **24**, 451.
Westlake, E. K. (1955). *Brit. med. J.*, **2**, 960.
Whitfield, A. G. W., Waterhouse, J. A. H. and Arnott, W. M. (1950). *Brit. J. soc. Med.*, **4**, 113.
Wilson, M. G. and Edwards, D. J. (1921). *Amer. J. Dis. Child.*, **22**, 443.
Wright, G. W. (1946). *Occup. Med.*, **2**, 546.

PORTAL HYPERTENSION IN FIBROCYSTIC DISEASE OF THE PANCREAS

BY

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It is now known that the liver is often damaged in fibrocystic disease of the pancreas. Bodian (1952) found patchy portal fibrosis and an increase in bile-duct structures, which he termed focal biliary fibrosis, in half of the 50 cases in his series in which histological sections of liver were available. This lesion is found most often and most severely in older children, but Claireaux (1956) has recorded similar findings in the liver of a newborn infant with fibrocystic disease. The livers in Bodian's series were not deeply scarred and there was little evidence of portal hypertension. Pugsley and Spence (1949) reported a grossly nodular liver in fibrocystic disease with a normal spleen, but in a series of 116 patients with the disease Webster and Williams (1953) noted splenic enlargement in the five cases with clinical evidence of cirrhosis. Di Sant' Agnese (1955) recorded two instances of cirrhosis and portal hypertension among a number of cases with normal or partial pancreatic function, and a recent leading article in the *British Medical Journal* (1956) also draws attention to this complication, but it is rare. In the case presented here great enlargement of the spleen resulted from portal hypertension and necessitated treatment, although the primary condition was otherwise in a satisfactory state of control.

Case Report

A boy of 9 years was admitted to the Royal Belfast Hospital for Sick Children on October 17, 1956, for investigation of hepatosplenomegaly which had been discovered at a routine school medical examination. He weighed 56½ lb. and was a bright, energetic and intelligent school boy and had no complaints about his health. He is an only child and his careful and attentive mother remembered that when he was about 10 months old he had bulky, pale and offensive stools for a few weeks, but was healthy thereafter. His development continued but was slightly delayed. He had an attack of measles in 1952 and following this a moderately sharp attack diagnosed as 'pulmonary congestion' from which he made a rapid and apparently complete recovery.

In July, 1953, at the age of 6, he was diagnosed as having coeliac disease. He had a distended abdomen, was under weight (36½ lb.) and passed frequent pale, bulky, greasy, foul-smelling stools. Trypsin was detected in the duodenal juice at 1/2,048 dilution. The stools contained 43·4 g. % fat (39·1 unsplit); the haemoglobin was 61% (Haldane). Neither chest nor alimentary radiographs showed any abnormality but clinically he was thought to have mild bronchitis. The liver was palpable 1 inch below the costal margin. The spleen was not felt. He was treated by a gluten-free, high-calorie, high-vitamin diet and, though not under any medical supervision, was free of complaints until the present admission to hospital in October, 1956.

On examination he was pale and the skin generally was slightly and patchily pigmented especially over the moderately protuberant abdomen. There was no jaundice; the fingers showed moderate clubbing. The liver was firm and easily palpable 2 inches below the costal margin. The spleen was large, firm and mobile, without pain; it reached to the mid-line and to the level of the umbilicus. Umbilical venous connexions were not detected on looking or listening and there was no evidence radiologically of oesophageal varices. There were no telangiectases and no nervous or other signs of hepatic failure. Plasma proteins and a bromsulphthalein test were within normal limits; zinc-sulphate flocculation was 5 units (normal 2.0) and serum alkaline phosphatase 43 K.A. units (normal up to 10). Seventy-two per cent. of an average fat intake was absorbed. Confirmation of the present diagnosis of fibrocystic disease was provided by the raised sweat electrolytes, namely sodium 113 mEq./l (normal 10-80) and chloride 122 mEq./l (normal 4-60). An attempt to obtain another specimen of duodenal juice was not successful. The chest showed signs of chronic bronchial infection clinically and radiologically. Glycosuria has never been found. Percutaneous splenic venography on November 6 showed a widely patent splenic vein without any of the tortuosity often seen in portal hypertension. In a portion of liver obtained by needle biopsy at the same time a moderate degree of fibrosis was found in some of the portal tracts which suggested that the splenomegaly was due to intrahepatic portal obstruction. The biopsy was similar to the subsequent one which is described below.

Laparotomy was carried out on November 23, and the

liver was found to be moderately enlarged and much firmer than normal. There was a diffuse irregularity of the surface suggestive of widely distributed patches of scarring, but gross nodularity was not present. The portal venous system was prominent and the pressure in one of the inferior mesenteric radicles was 275 mm. of saline, normal values by this method being up to 200. The spleen was grossly enlarged, firm and congested. There was no free fluid in the peritoneal cavity. Splenectomy was performed. The pancreas was of normal size but unduly firm. Scattered over its surface were a number of nodular areas of lighter colour resembling foci of fat necrosis and one of these was removed for microscopical examination as well as a further needle biopsy of the liver. The gall bladder was normal. The patient recovered well from the operation but his convalescence was interrupted by a pulmonary infection. For nine days he had pyrexia, cough and sputum. It cleared up with tetracycline and it has not recurred.

Two months after operation he was very well and happy at school.

Pathology. The spleen (710 g.) was fleshy and had small depressions on its surface. Section showed many rust-coloured areas of irregular outline surrounding small arteries (Fig. 1) and containing a large proportion of fibrous tissue. These iron-incrusted Gamna-Gandy bodies stood out conspicuously against the rest of the splenic tissue, which showed other features of fibro-congestive splenomegaly. The portion of pancreas removed presented several peculiar histological features. It was characterized by extensive microcystic dilatation of the ducts and by numerous hyperplastic islets which were often partly traversed by ductules (Fig. 2). Acinar tissue with zymogen granules was present in small amounts (Fig. 3) but most of it appeared to have been lost; the fibrous tissue was moderately increased in amount. There was no inflammatory infiltrate. The ducts contained eosinophil masses of roughly laminated matter denser than normal secretion. The liver biopsy showed a marked degree of fibrosis of some of the larger portal tracts; other and smaller tracts in the biopsy were normal. The fibrous areas had well defined oval outlines and in some instances the portal vein seemed narrowed; there was a minor lymphocytic infiltration and a dilatation of small blood vessels. Small bile ducts were more numerous than normal in the fibrosed tracts but well differentiated. In one instance a number of dilated small ducts were grouped together (Fig. 4) suggesting focal biliary obstruction. Occasional fibrous strands were seen running from one tract to another dividing the parenchyma irregularly; this was associated with an early stage of nodular regeneration of the parenchyma. There was no fatty infiltration.

Discussion

The scarring of the liver seen at operation was patchy and resembled that illustrated by Pugsley and Spence (1949) and by Webster and Williams (1953), although the process was more advanced in those fatal cases. In the fibrosed portal tracts small bile ducts were increased in number, though not to such a great extent as may occur in other forms of cirrhosis. Bodian (1952) considered an increase in bile-duct structures an essential element in the development of focal biliary fibrosis and explained the pathogenesis on the basis of localized obstructions of the bile ductules. Though our patient was not jaundiced, the elevation of the serum-alkaline phosphatase level, together with a less marked deviation of the zinc-sulphate-flocculation test, suggests some degree of biliary obstruction. Microcystic dilatation due to such an obstruction was seen in one of the biopsies and the process is illustrated also in the case of Pugsley and Spence (1949) where inspissated secretions plugged small ducts in the liver and where the gall bladder showed comparable changes. Fatty infiltration was absent in both of the biopsies taken here. Bodian (1952) found the incidence of fatty liver no greater in necropsies on fibrocystic disease than in fatal cases of other diseases and the evidence is against the view that fibrocystic disease brings about liver damage by causing a prolonged fatty infiltration. Fatty infiltration follows loss of the exocrine pancreas in animal experiments (Allan, Bowie, Macleod and Robinson, 1924) and in human disease such as congenital hypoplasia of the exocrine pancreas (Clarke and Hadfield, 1924; Davie, 1938) and lithiasis of the gland (Sanes, Miller, Brason and Geist, 1950). The infiltration leads in turn to a fine diffuse fibrosis (Chaikoff, Connor and Biskind, 1938; Himsworth, 1947; Sanes *et al.*, 1950). The train of events in fibrocystic disease, however, is quite different and it is clear that the patchy scarring of the liver in cases like the present one is not caused simply by pancreatic deficiency. Indeed, when cirrhosis is present the function of the pancreas is often remarkably preserved and active exocrine tissue seems to persist longer than in the majority of cases of the disease. In the present instance three years before splenomegaly was detected tryptic activity was so high in the duodenal juice that a diagnosis of fibrocystic disease was not made then. The liver, however, was palpable and lesions were probably present at that time. Two out of Webster and Williams' (1955) five cirrhotic cases and both of the cases of Di Sant' Agnese (1955) also showed considerable tryptic activity in the duodenal juice and in one of the latter the gradual onset of the pancreatic failure was traced by serial estimations. A biopsy taken from that patient while pancreatic function was still adequate showed a relatively normal gland with an increased amount of fibrous tissue and an early inflammatory reaction. Despite

FIG. 1.—The enlarged spleen. Irregular brown areas containing fibrous tissue and haemosiderin (Gamna-Gandy bodies) surround blood vessels. The red pulp is greatly increased. The surface is finely puckered ($\times 1\frac{1}{3}$).

FIG. 2.—Pancreatic biopsy. In this nodule the ducts are dilated and contain dense laminated material. Islet tissue is hypertrophied, fibrous tissue is moderately increased and acinar tissue is greatly reduced. There is no inflammatory exudate (haematoxylin and eosin $\times$ 85).

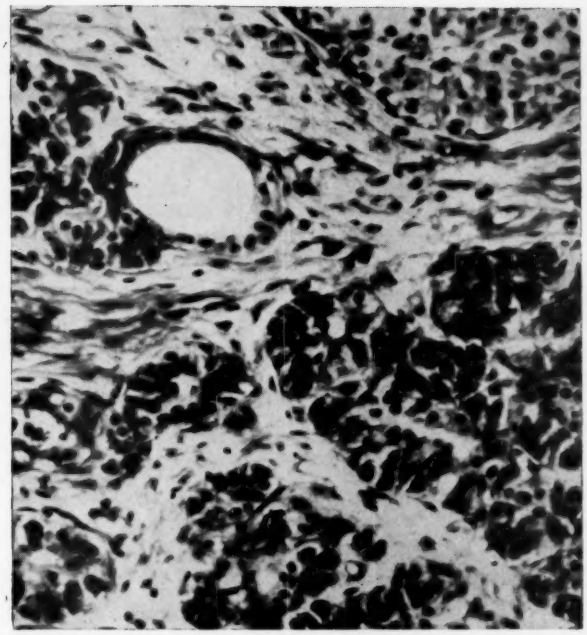

FIG. 3.—Pancreatic biopsy. An hypertrophied islet is shown, top right, and below it a dilated duct. Fibrous tissue is increased. Acinar tissue, present in much of the field, is somewhat atrophied (Mann's stain $\times$ 150).

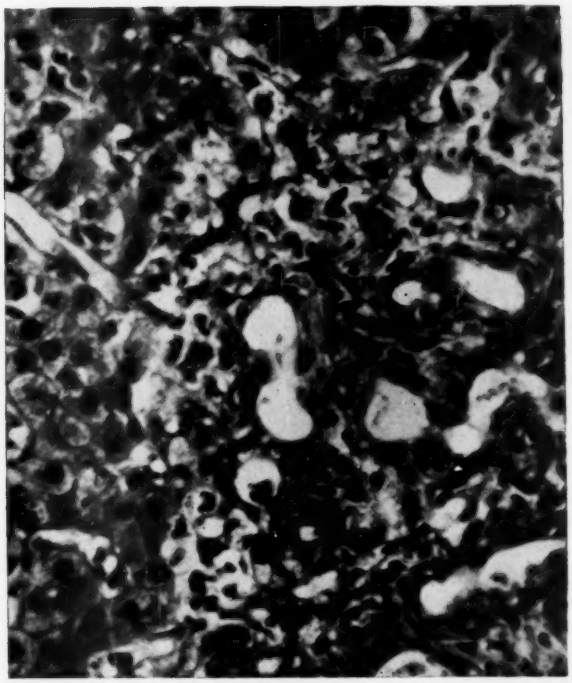

FIG. 4.—Liver biopsy. In this portal tract, bile ducts are increased in number and dilated. There is an increase in fibrous tissue and in the vascularity of the tract and a minor lymphocytic infiltration. Liver tissue, top and left, shows no marked changes here. (Haematoxylin and eosin $\times$ 400).

the biopsy finding of inflammatory changes in their own case the authors favour the view that blockage of the pancreatic ducts by inspissated secretions precedes degeneration of the parenchyma. The histology of the biopsy in our case, which tends to confirm this view, is of interest in showing dilatation of the ducts and inspissated secretions in a portion of the pancreas of a child whose pancreatic function was relatively good three years before. It apparently represents an intermediate stage in the evolution of the pancreatic lesion, and the absence of inflammatory reaction and the relatively minor degree of fibrosis are noteworthy. The hyperplasia of islet cells cannot be explained fully, though no doubt loss of acinar tissue has concentrated the surviving islets. It is not clear how this phenomenon is related to the main process but it probably accounts for the nodularity of this piece of tissue seen at operation. The biopsy differs in this and other points from the usual specimens removed at necropsies on younger patients. The pancreas in the case of Pugsley and Spence (1949), a 17-year-old boy, also showed unusual features. It is not to be expected that lesions first developing in the mature pancreas of the older child with cirrhosis would take the same form as those in the immature organ of more severely affected children in infancy. While some form of duct obstruction would appear to be essential to the pathogenesis of the pancreatic lesion of all ages, the presence of inflammation probably hastens its development as Claireaux (1956) suggests.

The fibrocystic changes in the pancreas are only part of a general upset of the exocrine glands of the body, and the introduction of sodium and chloride determinations as a diagnostic procedure (Di Sant' Agnese, Darling, Perera and Shea, 1953) has allowed atypical forms of the disease like that reported here to be recognized during life. Cirrhosis has been added to the dangers to which the patients are exposed but even in such cases it is respiratory infection which probably remains the most serious threat, generally causing death before liver function is grossly affected. Plasma protein levels and the bromsulphthalein were normal in the present case and similar findings are reported by Webster and Williams (1953) and Di Sant' Agnese (1955). The liver lesion, though progressive, has had more serious effects up to date on the portal circulation than on the liver cells and the possibility of haematemesis is as great as in any other type of portal hypertension. The spleen was larger than any we have seen in portal obstruction at this age, and though traumatic rupture is uncommon in portal hypertension, the organ was considered a danger to this patient who is an active schoolboy.

Di Sant' Agnese (1956) recommends a shunt operation for portal hypertension in fibrocystic disease but a splenectomy was considered adequate in the present instance because oesophageal varices had not been demonstrated, and because of our relatively favourable experience of the simpler operation in portal hypertension. A shunt may be performed at a later date.

Summary

A case of fibrocystic disease is reported in a 9-year-old boy in which gross splenomegaly resulting from cirrhosis and portal hypertension was treated by splenectomy. The fibrocystic disease had progressed slowly and a specimen of duodenal juice taken three years previously showed considerable tryptic activity. A respiratory infection was present and the diagnosis was confirmed by examination of sweat.

Biopsy of the pancreas showed unusual histological features but also marked dilatation of the ducts and inspissation of secretions.

Biopsies of the liver did not show any fatty infiltration of that organ; cirrhosis in fibrocystic disease is not brought about in this way and is not simply the result of destruction of the exocrine pancreas. Biopsies and liver function tests suggest that focal obstruction of bile ductules is the prime lesion. The main danger of liver disease in this condition is portal hypertension.

We are indebted to Dr. Muriel Frazer under whose care the patient came first, for kindly making her case notes available. We also wish to thank Professor J. H. Biggart for help and advice and Mr. D. Mehaffey for the photomicrographs.

References

Allan, F. N., Bowie, D. J., Macleod, J. J. R. and Robinson, W. L. (1924). *J. Exp. Path.*, **5**, 75.
Bodian, M. (1952). *Fibrocystic Disease of the Pancreas*, pp. 104-110, London.
British Medical Journal (1956). Leading article, **2**, 648.
Chaikoff, I. L., Connor, C. L. and Biskind, G. R. (1938). *Amer. J. Path.*, **14**, 101.
Claireaux, A. E. (1956). *Archives of Disease in Childhood*, **31**, 22.
Clarke, C. and Hadfield, G. (1924). *Quart. J Med.*, **17**, 358.
Davie, T. B. (1938). *J. Path. Bact.*, **46**, 473.
Di Sant' Agnese, P. A. (1955). *Pediatrics*, **15**, 683.
—— (1956). *J. Amer. med. Ass.*, **160**, 846.
——, Darling, R. C., Perera, G. A. and Shea, E. (1953). *Pediatrics*, **12**, 549.
Himsworth, H. P. (1947). *Lectures on the Liver and its Diseases*, p. 54. Oxford.
Pugsley, M. E. and Spence, P. McK. (1949). *Ann. intern. Med.*, **30**, 1262.
Sanes, S., Miller, D. K., Brason, F. W. and Geist, O. B. (1950). *Arch. intern. Med.*, **85**, 980.
Webster, R. and Williams, H. (1953). *Archives of Disease in Childhood*, **28**, 343.

ACCIDENTAL DIGOXIN POISONING IN A CHILD OF 2 YEARS

BY

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In view of the rarity of reports on 'digoxin' poisoning in children the following case is described.

Case Report

The patient, a healthy boy aged 2 years, was first seen in the Casualty Department where the mother gave a history of his having swallowed some 29 0·25 mg. tablets of 'digoxin' an hour previously. The tablets were unsweetened and had an unpleasantly metallic after-taste. His stomach was promptly washed out, the washings showing no obvious fragments of tablets, and a dilute solution of tannic acid was instilled. At this stage the child's general condition was perfectly normal but he was nevertheless admitted to the ward. Clinical examination and electrocardiography at this time were both normal, the heart rate being 112 a minute, with a normal sinus rhythm.

Four hours after the ingestion of 'digoxin' there began a change in the child's condition. He started to vomit, both spontaneously and when given fluids, and the pulse rate began to fall. Twelve hours after admission the pulse rate and the apex rate were both 60 a minute and an E.C.G. showed heart block with an auricular rate of 120 and a ventricular rate of 60, though the characteristic RT segment and T wave changes of digitalis were not apparent.

Vomiting continued intermittently for two days but subsided spontaneously. The bradycardia accompanied by a strong radial pulse persisted for four days.

During the period of intoxication careful observation was maintained for the onset of peripheral circulatory failure and of cardiac failure, and repeated E.C.G. tracings were made to detect as early as possible the development of ventricular irritability.

For four days the child lay quietly in bed, but, on the fifth day after admission, corresponding with a change in the cardiac rhythm to a sinus bradycardia, he became more active.

The patient was discharged 10 days after admission when clinical examination and an E.C.G. revealed no abnormality.

Discussion

Schneeweiss (1952) described a case where a boy of 3 years swallowed 70 0·25 mg. tablets of 'digoxin'. Though, as in the case described above, the stomach was washed out within an hour, within three hours the child's pulse rate slowly dropped and became irregular. He was unable to obtain tracings of the arrhythmia but treated the patient with comparatively large doses of atropine by subcutaneous injection and oral quinidine. Complete recovery took place.

Magidson and Suffern (1952) described a case where a boy of 3 years swallowed 30 0·25 mg. tablets of 'digoxin' together with six 'fersolate' tablets and four compound codeine tablets. Vomiting began nine hours later, a delay due perhaps to the codeine, and continued for 24 hours before medical aid was sought. On admission to hospital, stomach and bowel were washed out. An E.C.G. showed partial heart-block and marked RT segment and T wave changes. This case was treated with 1/150 grain atropine sulphate and coramine. An E.C.G. the following day showed a normal rhythm though RT segment and T wave changes persisted. Five days after ingestion the E.C.G. was normal.

Early on in the management of the present case it was decided to withhold specific treatment until the onset of cardiac or peripheral circulatory failure or the development of ventricular irritability. In deciding upon this course we were influenced by the lack of satisfactory evidence as to the safety and the efficiency of the drugs available.

On theoretical grounds the treatment of ventricular irritability would be either by quinidine or by procaine amide. However, there are cardiologists who, having treated patients with heart block developing ventricular arrhythmias with procaine amide (Wedd, Blair and Warner, 1951) and quinidine (Di Palma and Schultz, 1950), declare them to be either ineffective or dangerous. Robbin, Goldfein, Schwartz and Dack (1955) suggest that in the presence of heart block when asystole, ventricular tachycardia or fibrillation develop, isoprenaline is the drug of choice.

As it turned out, the patient was well able to deal with the problems posed by heart block without the help of specific agents.

The present case stresses the importance of thorough and early gastric lavage in spite of a child's good condition as the value of later treatment is so doubtful. Subsequent treatment should be governed by the clinical state and repeated electrocardiograms.

Summary

A case is described where a child swallowed 7·25 mg. 'digoxin' and survived, though heart block persisted for four days.

The treatment of 'digoxin' poisoning is considered.

I am grateful to Dr. P. N. Swift, consultant paediatrician, Orpington Hospital, for permission to report this case and for his helpful comments.

References

Di Palma, J. R. and Schultz, J. E. (1950). *Medicine* (*Baltimore*), **29**, 123.
Magidson, O. and Suffern, W. S. (1952). *Univ. Leeds med. J.*, **1**, 125.
Robbin, S. R., Goldfein, S., Schwartz, M. J. and Dack, S. (1955). *Amer. J. Med.*, **18**, 577.
Schneeweiss, J. (1952). *Med. J. Aust.*, **2**, 37.
Wedd, A. M., Blair, H. A. and Warner, R. S. (1951). *Amer. Heart J.* **42**, 399.

BRITISH PAEDIATRIC ASSOCIATION

Proceedings of the Twenty-eighth Annual General Meeting

The twenty-eighth meeting of the British Paediatric Association was held at the Old England Hotel, Windermere, from May 1 to 4, 1957.

BUSINESS PROCEEDINGS. Professor John Craig took the Chair as President, and the following members were present:

F. M. B. Allen, E. C. Allibone, I. M. Anderson, J. Apley, Cecile Asher, M. Bodian, Frances Braid, J. V. Braithwaite, P. T. Bray, G. Brewis, F. S. W. Brimblecombe, R. W. Brookfield, D. Browne, W. A. B. Campbell, I. A. B. Cathie, N. S. Clark, T. Colver, D. Court, W. S. Craig, E. Mildred Creak, J. Crooks, V. Mary Crosse, G. Davison, D. M. Douglas, A. C. Doyne Bell, S. Dundon, R. W. B. Ellis, J. L. Emery, P. R. Evans, J. O. Forfar, Isabella Forshall, A. White Franklin, D. Gairdner. W. Gaisford, W. H. Galloway, C. F. Harris, C. C. Harvey, J. D. Hay, W. Henderson, A. Holzel, D. V. Hubble, F. P. Hudson, J. H. Hutchison, Ursula James, H. Jolly, H. Everley Jones, G. M. Komrower, R. Lightwood, J. Lorber, R. Mayon-White, P. MacArthur, D. MacCarthy, Agnes Macgregor, Helen Mackay, R. Mac Keith, R. A. McCance, R. McIntosh, T. Mann, F. J. W. Miller, A. A. Moncrieff, G. A. Neligan, G. H. Newns, A. P. Norman, J. N. O'Reilly, C. G. Parsons, W. H. Patterson, W. W. Payne, C. P. Pinckney, C. T. Potter, K. B. Rogers, L. G. Scott, R. A. Shanks, W. Sheldon, Victoria Smallpeice, W. C. Smallwood, J. Forrest Smith, R. E. Smith, R. E. Steen, K. Tallerman, M. L. Thomson, J. P. M. Tizard, R. McL. Todd, H. C. Trowell, D. Waterston, A. G. Watkins, S. D. V. Weller, H. Parry Williams, T. Pearse Williams, B. D. R. Wilson, D. W. Winnicott, Winifred F. Young, S. Yudkin.

Professor Charles Dent (Still Lecturer) and the following Danish paediatricians attended as guests of the Association:

Dr. P. W. Braestrup (President, Danish Paediatric Society), Dr. K. Biering-Sorensen, Dr. E. Flamand Christensen, Dr. Paul Drucker, Dr. Carl Friderichsen, Dr. B. Friis-Hansen, Professor Preben Plum, Dr. A. Rothe-Meyer, Dr. Annie Schondel, Dr. O. Steinecke, Dr. E. Terslev, Dr. F. Tudvad, Dr. Jorgen Vesterdal.

The following were present as guests of members of the Association:

J. D. Allan, E. Back, J. Beveridge, P. J. N. Cox, Professor P. György, Ruth Harris, K. S. Holt, Jean Hutchison, W. Kennedy, W. B. MacDonald, P. L. Mollison, P. Masse, Nathalie Masse, D. Pullon, T. J. Rendle-Short, I. Schneideman, F. T. Shannon, Professor C. Salazar de Sousa, L. L. R. White, S. Yaffe.

The Annual General Meeting was held on May 2, 1957.

The Minutes of the last annual meeting were received and approved.

ELECTION OF OFFICERS. The following were elected:

PRESIDENT: Dr. K. H. Tallerman
PRESIDENT-ELECT: Dr. J. Forrest Smith
TREASURER: Dr. R. Lightwood
SECRETARY: Dr. P. R. Evans

EXECUTIVE COMMITTEE, 1957-60:
Dr. I. A. B. Cathie, Miss I. Forshall, Dr. F. F. Kane, Dr. M. MacGregor.

ELECTION OF MEMBERS. The following were elected:

HONORARY MEMBERS

Mr. Denis Browne, Professor John Craig, Dr. W. E. Crosbie, Dr. H. L. Wallace

CORRESPONDING MEMBERS

Dr. H. Bakwin (New York), Dr. S. Doxiadis (Athens), Professor R. Dubois (Brussels), Professor A. Ross (Montreal)

ORDINARY MEMBERS

Dr. R. Astley, Dr. K. W. Cross, Dr. H. L. Ellis, Dr. J. W. Farquhar, Dr. J. Jacobs, Dr. J. H. Moseley, Dr. P. E. Polani, Dr. A. Russell, Dr. T. Stapleton, Dr. W. Walker

3. The Treasurer's report was approved and the auditors were re-appointed for one year.

4. The Executive Committee's report was received and approved, and is printed below.

5. Rules 4, 11 and 17 were altered to read:

Rule 4. '. . . No candidate may be proposed for election to these offices unless his name, duly proposed and seconded, has been sent to the Secretary at least three months before the Annual Meeting.'

Rule 11. '. . . Any member of the Association may, by letter to the Secretary, not less than three months before the General Meeting, propose the name of a candidate and shall at the same time state the grounds of recommendation of the candidate . . .'

Rule 14. 'Notice of any proposal to amend or alter the existing rules, or to pass new rules, must be sent to the Secretary not later than three months before the next ensuing General Meeting, and must appear on the Agenda of the said Meeting in the form of a motion.'

6. After full discussion it was agreed that, while working within the framework of the present constitution, membership should be increased to take in the majority of hospital paediatricians, as well as other medical men and women with paediatric interests, within three years.

7. Dr. Sheldon asked the Executive Committee to review the status of fever hospitals in relation to paediatric units throughout the country.

Report of the Executive Committee, 1956-1957

1. The Association will wish to congratulate Dr. John Hay on his appointment to the Chair of Child Health in the University of Liverpool, and Mr. Denis Browne on the award of the Ladd Medal. No doubt others have been honoured and the Executive must apologize for not noticing all the lights under the bushels.

2. REPORTS, ETC. During the year two reports have been published: one the annual report of investigations into prematurity, which are being carried out in many parts of the country; the other, the report on hypercalcaemia which appeared in the *Lancet* and the *British Medical Journal*. Since publication of the latter report, the vitamin D content of some cereal foods has been reduced.

Two further reports have been completed and await publication. One on radio-iodine deals with the precautions which may be taken to evade the somewhat remote chance of producing carcinoma of the thyroid by investigations in which radioactive iodine is used. Another, on hospital accommodation for children, is separate from, but somewhat complementary to, the report produced by the Paediatric Committee of the Royal College of Physicians of London, and it is hoped that the two reports will be published at about the same time. As a consequence of discussion of this subject an attempt is being made to find out how many children are being nursed in adult wards, a topic of special interest in regions where the closure of children's units to provide adult beds has been proposed.

In addition to these reports, a sub-committee has prepared written evidence for submission to the Cranbrook Committee on Maternity Services, and another sub-committee has, at the request of the Division of Architectural Studies of the Nuffield Foundation, considered the Registrar General's diagnostic classification.

Other subjects under consideration are special clinics (such as chest clinics and epilepsy clinics) and a large survey of perinatal mortality to be carried out under the auspices of the National Birthday Trust Fund.

3. GUESTS. A dinner for about 200 people was held by the Association and the American Academy of Pediatrics at the Mansion House in London just before the opening in July of the very successful international congress in Copenhagen, which was attended by many of our members. We are extremely glad to welcome our Danish guests at our annual meeting this year.

4. JAMES SPENCE MEDAL. The James Spence Memorial Committee has decided that a gold medal shall be presented from time to time in recognition of outstanding contributions to the advancement or clarification of paediatric knowledge. The Committee has asked the Association to make the award and has allocated £2,000 to the project. The Executive has thanked the Memorial Committee for its confidence and generosity, and is proceeding with the preliminary legal arrangements.

5. WINDERMERE LECTURE. The endowment of this lecture ended last year, but the board of directors of Messrs. Cow & Gate has renewed the endowment until further notice.

6. THE HISTORY AND THE ALBUM. One hundred and fifty-two copies of Dr. Cameron's history of the first 25 years of the Association have been sold, and 40 presentation or review copies given away.

Dr. George Davison has been raised to the dignity of Curator of the Album. and will be pleased to receive photographs of B.P.A. events or persons.

7. STANDING COMMITTEES. Membership of the standing committees has been reviewed and re-cast more than usual. The Convalescent Homes Committee (joint with the I.C.A.A. and the Institute of Almoners) and the Tuberculosis Committee have been dissolved as they had not met for a long time. Professor Gaisford continues to represent us on the Joint Tuberculosis Council and Dr. Evans is our representative on the new National Committee on Poliomyelitis.

The Child Psychology Committee has been particularly active. The Underwood Report on Maladjusted Children suggested that to meet the needs the number of children's psychiatrists ought to be doubled (to 170), of children's psychologists doubled too, and of psychiatric social workers quadrupled. The committee wonders whether a paediatric training plus an analysis might not be a better equipment for a children's psychiatrist than the usual D.P.M. course, and it would like to discuss this with the Children's Psychiatry Section of the Royal Medical-Psychological Association. The Committee has asked all paediatricians for their views on the psychiatric services for children and adolescents. Too often there seems to be inadequate liaison with a paediatrician. The need for in-patient

facilities is the subject of a recent memorandum of the Royal Medical-Psychological Association at present under review. The facilities for training students, registrars, paediatricians and other doctors need to be increased and the Postgraduate Federation has been approached, though each region will probably make arrangements. Preventive hygiene in maternal and child welfare clinics, the modifications in the law relating to children, and the procedures for dealing with educationally subnormal children have been under consideration. The Royal Medical-Psychological Association asked the B.P.A. to suggest speakers for a meeting on psychological factors in the causation of attacks of epilepsy. The committee hopes that the 1958 B.P.A. programme will include a discussion on a psychiatric or psychological aspect.

8. MEMBERSHIP. The Executive Committee has discussed policy regarding future membership of the Association at length, and recommend that there should be an increase, spread over five years, to include almost all established paediatricians as well as a leavening of paediatric surgeons, pathologists, physiologists, etc.

9. SPECIAL MILK FOODS. Some members have had difficulty in obtaining low-calcium or lactose-free milk foods by N.H.S. prescription. They should be obtainable on the ground that milk preparations used for specific treatment in certain diseases can be classed as drugs (see 1950 report of the Cohen Committee—The First Report of the Definition of Drugs Joint Sub-Committee of the Standing Medical, Pharmaceutical and General Practitioner Advisory Committees). The firms concerned have been informed by the Ministry of Health that everything possible has been done to arrange that prescriptions of these preparations will not be questioned.

George Frederic Still Memorial Lecture

Professor Charles Dent (London) delivered the Still Lecture, entitled 'Hartnup Disease: An Inborn Error of Metabolism', of which the following is a summary.

Our investigations on this disease (also called H. disease by Baron, Dent, Harris, Hart and Jepson, 1956) began in the year 1951, when a patient of a most interesting family (who have kindly agreed to give their name to the disease) was studied under Dr. E. W. Hart at the Middlesex Hospital. This patient was suffering from a rash apparently identical to that of pellagra and had in addition neurological signs of cerebellar ataxia. The rash had followed exposure to the sun, but true pellagra seemed an unlikely cause since there was an inadequate history of dietary deficiency. Furthermore Dr. Hart was suspicious of a more complicated metabolic upset since one of the patient's elder sisters had been previously admitted many years earlier with a seemingly identical disease, from which she had made a good recovery.

Of the many routine investigations done, nearly all gave normal results and the important negative ones were those which excluded any of the known porphyrias. Urine testing, however, showed the presence of a gross generalized amino-aciduria of quite unique pattern. Further investigation of metabolites of tryptophan was also undertaken in view of the pellagra-like disease and resulted in the discovery of a gross abnormality of indole excretion. The urine contained large quantities of indolylacetic acid, of indolylacetylglutamine (Jepson, 1956), of indican and moderate quantities of tryptophan itself. There was clearly a very interesting metabolic disorder present.

There were eight sibs in the family and the parents were first cousins. Routine urine testing showed that four out of the eight sibs had an identical urine abnormality with regard to the amino-acid and indole excretion. Of these four, the eldest was the sister who had previously been admitted with the diagnosis of pellagra: two others appeared clinically well but one of them had a mild degree of skin photosensitivity: the fourth was our presenting case.

The amino-aciduria was thoroughly studied on all four sibs and shown to be entirely of renal origin. No other defects of renal tubule function could be discovered. We do not yet know the mechanism of indole excretion, but presume that it is associated with high plasma levels and results from this excessive accumulation in the body. The indican output (but not that of the other indoles) could be greatly increased by feeding extra tryptophan and entirely prevented by giving chlortetracycline, even with simultaneous extra tryptophan in the diet.

Between the various sibs we have now observed many attacks of the disease. It takes the form of a pellagroid rash following moderate exposure to direct sunlight. When severe there are also added signs of cerebellar ataxia, which is usually very mild and variable but has been completely crippling and associated with delirium on a few occasions. Both skin and neurological signs are completely reversible in a month or so of conservative treatment. Whether the improvement has been hastened by simultaneous nicotinamide therapy still remains doubtful. On a few occasions a co-existent infection has precipitated neurological signs without there being any rash. An ominous further feature is that the three older affected sibs show mental retardation which is more severe in order of increasing age.

We were puzzled as to the relationship of this disease to true pellagra (of which we have only negligible experience). Reading the British literature on alleged cases of true pellagra, it appeared that this could be identical with the disease occurring in our family. The American literature on pellagra described, however, a rather different clinical picture since the neurological complications were rare, but, when present, more often resembled a peripheral neuritis and rarely, if ever, a pure cerebellar ataxia. We therefore became suspicious that

perhaps many of the British cases might in fact have been cases of Hartnup disease. As the gross and highly specific biochemical abnormalities in the urine seemed to be quite constantly present, independently of the co-existence or otherwise of the pellagra-like disease, it seemed that it would be easily possible to re-diagnose any case of British pellagra previously described, providing that urine could be obtained from the patient. We have been fascinated therefore to discover retrospectively that the cases described as of pellagra by Hickish (1955) and by Hersov (1955) do in fact excrete urine with an amino-aciduria and with indole abnormalities identical with that of the four sibs in our particular family. Two further cases are also recently described from Holland (Jonxis, 1957) and one from Germany (Dr. H. Bickel, private communication), and Drs. Philip Evans and W. Henderson have kindly provided me with details of a further case (unpublished) in a girl of 5 years admitted in 1952 to the County Hospital, York, and later to The Hospital for Sick Children, Great Ormond Street. In this last case the child had developed a rash following an attack of infective diarrhoea, but neurological signs later developed, suggesting the possibility of a cerebellar tumour. The rash was finally noted to be indistinguishable from that of pellagra and both it and the neurological signs became normal after two months of hospital treatment which included additional nicotinamide. The diagnosis of this child from the case summary was : 'A case of pellagra with skin involvement and ataxia, the cause of whose origin cannot be traced in the dietary history'—an excellent, if cautious, summary of the clinical findings in the light of the knowledge then existing. We obtained urine from her five years later at a time when she was quite well: it showed the usual gross abnormalities of Hartnup disease.

From what we have said already it seems clear that the disease can be considered as a further example of an inborn error of metabolism in the sense that this term was used by Garrod, and that it is caused by an autosomal Mendelian recessive gene. We have not definitely determined the biochemical mechanism which must be the main cause of the disease. It is of note that the clinical signs only occasionally develop in patients constantly showing this gross biochemical abnormality. It is nice to think that it may be concerned with a disorder of tryptophan metabolism whereby a metabolic block exists somewhere in the course of its transformation to nicotinamide. In this way the subject can be considered to be always in a state of inadequate nicotinamide nutrition and therefore to be readily toppled over into gross deficiency by any factor further decreasing its supply or increasing its metabolic requirement. The block must be very early in the metabolic sequence since the metabolites which seem to be accumulating all contain intact indole rings, only the side chain being altered. There is a strong resemblance here to the abnormality in phenylketonuria where, however, it is the benzene ring, not the indole ring, which cannot be broken down. The relationship of the amino-aciduria to the indole abnormality seems, however, to be very obscure. From here we are led on to rather intriguing thoughts as to the possible metabolic causes of diseases alleged on usually inadequate grounds to be due to so-called 'resistance' to vitamins or hormones such as, for instance, 'vitamin-D resistant' rickets or 'parathormone-resistant' hypoparathyroidism. By the same way of thinking, Hartnup disease could be considered as exemplifying 'nicotinamide-resistant' pellagra. We are entitled also to ponder further as to the possible nature of the hereditary factors which so often predispose to the development of many other diseases in which the immediate cause is clearly environmental, although insufficient in itself to have any effect on the majority of apparently normal people. Even in known cases of Hartnup disease the clinical signs are exceedingly inconstant and may manifest themselves in bizarre ways which would not be expected to lead to a correct diagnosis if arising for the first time in another subject. It may well be, therefore, that the biochemical disorder is fairly common and should be more actively sought. We are suspicious, for instance, of any patient who might present only with a photosensitive rash or only with acute (and fully reversible) cerebellar ataxia following febrile disease. Fortunately the diagnosis of Hartnup disease can be readily made retrospectively by examination of urine sent by post.

REFERENCES

Baron, D. N., Dent, C. E., Harris, H., Hart, E. W. and Jepson, J. B (1956). *Lancet*, **2**, 421.
Hersov, L. A. (1955). *J. ment. Sci.*, **101**, 878.
Hickish, G. W. (1955). *Archives of Disease in Childhood*, 30, 195.
Jepson, J. B. (1956). *Biochem. J.*, **64**, 14P.
Jonxis, J. H. P. (1957). *Ergeb. inn. Med. Kinderheilk.*, **8**, 195.

Scientific Sessions

RUTH F. HARRIS and J. P. M. TIZARD (London). 'Electroencephalography in the Normal and Abnormal Newborn.' An investigation had been carried out to try to establish normal standards for the electroencephalogram in newborn babies and infants, and to determine whether the electroencephalogram will assist in predicting the outcome of cerebral disturbances in the newborn.

The technique used is bipolar recording from six silver cup electrodes, one frontal, one occipital and a pair on either side of the head to straddle the motor cortex. The pulse and respiratory rate are recorded simultaneously. Recording is done when the baby is quietly awake and during normal sleep.

There is little rhythmical electrical activity in the waking baby but when asleep there are bilaterally simultaneous bursts of activity from central and frontal areas lasting 2-4 seconds every 4-8 seconds with relative inactivity between episodes. These episodes are not accompanied by movement or change in respiration. It is thought that they indicate a lightening of sleep due to some internal stimulus because similar episodes can be evoked by the external stimulus of noise, which, without rousing the soundly sleeping baby will, after a primary auditory response, produce a burst of electrical activity.

A general simplification of pattern is seen in the electroencephalogram of older babies with increasing amplitude and short runs of rhythmic 10-14 cycles per

second activity from the central areas. In the very immature infants electrical activity from the brain occurs intermittently.

From practical experience the following would be considered abnormal : Persistent focus or foci of sharp waves; spikes of high-amplitude rhythmic slow activity; marked asymmetry between the hemispheres or very low amplitude records. Most of these types of activity have been seen in clinically abnormal babies, e.g., in cases of cerebral haemorrhage, fits and anoxia.

Not all clinically abnormal babies have abnormal electroencephalograms.

It is possible that the electroencephalogram will be of some prognostic significance in later epilepsy.

O. STEINICKE (Copenhagen). 'Persisting Abnormal Pyloric Motility following Hypertrophic Pyloric Stenosis.' The author reported work done in collaboration with N. Roelsgaard.

Radiological examination of 45 adult persons (aged 25-45 years), who had suffered from hypertrophic pyloric stenosis in infancy and had been treated by stomach emptying exclusively, showed persisting abnormalities of pyloric motility in 78% of the cases; 14 of the 45 had developed gastric ulcers.

Patients whose hypertrophic pyloric stenosis had been treated with modern antispasm or surgical therapy showed a much earlier radiological return to normality of pyloric motility.

In regard to antispasmodic treatment, residual changes were found in 37% of 49 cases aged 7-11 years and 21% of 47 cases aged 12-18 years.

In regard to surgical treatment, residual changes were found in 43% of 30 cases aged 2-6 years and in 17% of 29 cases aged 7-11 years.

These figures indicate that a return to normal occurs earlier after surgical treatment than after antispasm therapy.

J. D. ALLAN (Stockport). 'A New Metabolic Disease.' This paper described the clinical features and preliminary investigations of a new disease.

The disease is essentially one of mental defect and constantly abnormal amino-aciduria in which epileptiform convulsions and temporary ataxia may occur. It is possible that a congenital heart lesion may be an additional anomaly and that clinical manifestations may not be apparent till some time after 1 year of age. This condition adds another to the list of metabolic disorders associated with mental defect.

The disease was described in two sibs. The urinary excretion of the abnormal amino-acid is constant. It is as yet unidentified. It has been demonstrated in urine, plasma and C.S.F. by chromatography. It is present in the cerebrospinal fluid in a much higher concentration than in the plasma from which it is cleared at the normal rate of glomerular filtration. Comment is made on certain physical characteristics, namely the facial appearance and the hair, and on the results of certain investigations, namely the E.E.G.s, the I.Q. rating, the blood groups, the pedigree and family and the alkaline phosphatase.

It is considered that the disease is probably of hereditary linkage and that its chief importance is in its relationship to the further elucidation of the causes of mental deficiency.

P. W. BRAESTRUP (Copenhagen). 'Personal Experiences in Starch Intolerance in Childhood.' Twenty-five cases of starch intolerance in children from 1 to 8 years were observed in two years compared with four regular coeliac syndromes.

In 16 cases examined, radiographs demonstrated pathological segmentation and dilatation of the ileum as seen in the coeliac syndrome and sprue.

As all cases responded favourably to diet restricted alone in gluten, gluten intolerance would be a more adequate term.

Growth intensity was impaired before treatment in all cases where data were available, whereas most cases showed considerable increase above average in growth intensity on adequate dietary restrictions.

P. L. MOLLISON (London) and W. WALKER (Newcastle-upon-Tyne). 'The Cause of Death in Haemolytic Disease.' The mortality in liveborn infants with haemolytic disease of the newborn can be reduced to less than 5% by the proper use of exchange transfusion; this implies that the total number of deaths in England and Wales should not exceed 150 a year. The fact that the number registered remains about 400 prompted the present enquiry.

Of the 400 cases certified as dying from haemolytic disease of the newborn each year, 100 died from some other cause, the commonest being kernikterus of prematurity. Amongst the 300 cases dying from haemolytic disease of the newborn, failure of antenatal prediction and failure to carry out an adequate exchange transfusion were very common.

PREBEN PLUM (Copenhagen). 'Experiences with Drug Therapy in Cerebral Palsy.' In a clinical search for a useful skeletal muscular relaxant in cerebral palsy we have noticed a surprisingly good effect of mysoline (5-ethyl-dihydro-5-phenyl-4·6-(1 H, 5 H)-pyrimidinedione) in athetosis. In 18 of 31 cases of athetosis the effect was good; in spastic patients there was some effect in some cases, but it was less convincing. Mysoline was used in doses much smaller than usual in the treatment of epilepsy, most often 25 mg. three times a day.

P. J. N. COX (London). 'Metabolic Studies in the Syndrome of Virilising Adrenal Hyperplasia with Salt Loss.' Sixteen cases of virilizing adrenal hyperplasia with an associated salt-losing syndrome have been seen at The Hospital for Sick Children, Great Ormond Street, in the past five years. Five of them have died, three are being treated elsewhere and eight are still attending the hospital.

With the increasing study of infants who fail to thrive in the first few months of life, some difficulties have been encountered in the early diagnosis of the disease in boys, who at this stage show no evidence of virilization.

The physiological basis of the electrolyte imbalance is poorly understood, and five cases have received special study from this point of view.

It has been found by others that A.C.T.H. aggravates the sodium loss; and it has, therefore, been suggested that the hyperplastic adrenal produces an abnormal hormone which prevents reabsorption of sodium in the renal tubule. It is now shown that the effect of A.C.T.H. is variable, and that inhibition of the secretion of A.C.T.H. by the administration of prednisolone may aggravate the disease instead of leading to improvement as might have been expected. The interpretation of these findings is discussed.

BENT FRIIS-HANSEN (Copenhagen). 'Body Water Equilibrium during Weight Reduction and Changes in Body Composition.' In a number of obese children the volume of total body water was measured by the heavy water method, extracellular fluid being estimated by the thiosulphate method. The intracellular fluid may then be calculated by subtraction.

In the fat children these body water compartments were lower than normal, when calculated as a percentage of body weight.

The volumes decreased only by 1-2% during an average weight reduction of 16%, indicating a loss of pure fat tissue (allowing for a slight growth during the observation period).

From these observations the amount of fat tissue in the body may be calculated before and after weight reduction. This is compared with the degree of overweight and the weight loss.

T. J. RENDLE-SHORT (Sheffield).'Infant Management in the Eighteenth Century.' Before 1700 infant care was a mixture of folklore and ancient Greek empiricism. The eighteenth century marks the first movement towards infant management.

For this paper all the available English textbooks and pamphlets on the management of children published in the eighteenth and early nineteenth centuries have been consulted (they number about 30). The paper shows the development of ideas on such matters as the management of the newborn, clothing infants, sleep, teething and infant feeding.

F. TUDVAD (Copenhagen). 'The Status of Prophylactic Vaccinations in Danish School Children.' The extent to which the public will avail themselves of the free vaccinations against smallpox, diphtheria, tuberculosis, and poliomyelitis, which is open to all Danish children, was discussed. The figures, all of which refer to the school year 1955-56, include all Danish schoolchildren (634,300 from 4,037 schools), show the possibility of having at least 90% of all Danish schoolchildren vaccinated on a voluntary basis.

L. L. R. WHITE and M. BODIAN (London). 'The Treatment of Neuroblastoma with Vitamin B_{12}.' Conventional modes of therapy have only a restricted application in the treatment of neuroblastoma because of the high incidence of tumour spread at presentation.

It has been found empirically that prolonged treatment with vitamin B_{12} in massive dosage leads to regression of the tumour in a significant proportion of cases.

To date a total of 29 children have been so treated. Regression of the tumour was observed in 50% of these patients, and 25% are alive and well one and a half to six years from the onset. This favourable response was virtually limited to cases presenting in infancy.

K. S. HOLT (Sheffield). 'The Siblings of Mentally Retarded Children.' The adverse effects of mentally retarded children upon their siblings have been studied by visiting families with retarded children in Sheffield. In 169 families there were normal children in addition to those retarded. These siblings were considered in four groups: those younger than the defective child and either below, or of school age, and those older and either of or past school age.

The observations about those children older than the defective child and past school age were incomplete as many had left home, but between 20 and 24% of the siblings in the other groups were seriously disturbed by the retarded child.

There were 66 affected children from 57 families. Thus, in a third of the families visited there was at least one normal child affected adversely by the defective child.

Twenty-four children suffered physical attacks; 20 resented the attention given to the retarded child; 11 suffered through the help they had to give in the home; and 10 were ashamed and embarrassed by the defective child.

Inadequate parental care led to attacks, whilst excessive devotion to the handicapped child led to resentment and jealousy.

The effects upon the siblings caused 13 retarded children to be admitted to an institution, with benefit to the normal children.

Removal from home of the retarded children may not be the only solution of the difficulties and possibly fewer problems would arise if more help were given to the family as a whole.

BOOK REVIEWS

Advice to the Expectant Mother. By F. J. BROWNE and J. C. MCCLURE BROWNE. (Pp. 46+Index. 1s.) Edinburgh and London: E. & S. Livingstone.

This excellent little pamphlet is now brought out in its eleventh edition and remains what it has always been, a well written and very useful aid to mothers who are about to have their first baby.

The neonatal and antenatal paediatric advice is up-to-date in conception and description, and it might well be distributed to all mothers by a benevolent Welfare State.

Your Baby—and You. By WINIFRED DE KOK. (Pp. 221; illustrated. 2s. 6d.) London: Pan Books. 1957.

This small paper-covered book, by a medical grandmother sets out to inform a young expectant mother, living in this country, of what might be called the routine happenings she may anticipate as regards the course of pregnancy and labour, antenatal care, care in hospital, and postnatal care, as well as the normal development and behaviour of her infant. In addition, it provides practical advice on measures needed for her own health and on infant and child care. A considerable part of the book is factual, and the teaching provided would meet with the approval of most paediatricians, in general if not in every detail, since opinions inevitably differ. In the reviewer's opinion it is a book which would be appreciated by very many young women experiencing their first pregnancy.

The Health of the School Child. Report of the Chief Medical Officer of the Ministry of Education for the Years 1954 and 1955. (Pp. 187. 6s.) London: H.M. Stationery Office. 1957.

This represents a budget on school health. The gains are obvious and there is clearly a growing balance on the credit side. Heights and weights for corresponding ages continue to creep up for both sexes and adult stature is reached at an earlier age than formerly. In October, 1955, nearly half the children in State schools were taking school dinners and 85% were having school milk. Unfortunately it is the children classed as 'unsatisfactory' from the physical standpoint that often have neither the dinners nor the milk. A paragraph on 'obesity' indicates that the nutritional problems of today are different from 50 years ago! Although special investigations in certain areas are reported there is not enough research nor of the critical approach to remaining problems in the school health field. There are several pages on postural defects and remedial work but no hint that some of these 'defects' may be physiological variants of growth for which no treatment is necessary. A control series would soon settle whether this statement is true or not, and according to tables on page 174 more children with postural defect were 'observed' than 'treated' so that the material is presumably available. It is also a matter of some concern that less than half the children examined on entering school have a 'general condition' classified as 'good', the other half being 'fair' and about 2% 'poor'.

Le Mensonge Chez L'Enfant. By JEAN-M. SUTTER. (Pp. 170. Fr. fr. 480.). Paris: Presses Universitaires de France. 1956.

A man went to church. He said the parson preached on sin. When asked what the parson said, he replied: 'I don't know, but he was agin' it.' The author of this book is agin' lying.

The main thesis of the book is acceptable—that parents and educators would do well to understand why a child lies instead of blindly reacting. It seems that adults get het up by children's lies, and give 'correction exemplaire, à main nue ou, armée d'un fouet, d'une cravache, d'une ceinture . . .', and sadism infinitely multiplies the resources of the imagination.

Unfortunately the author has no understanding to give. Instead he classifies the various kinds and degrees of lying.

The author has been untouched by the discoveries of the past 50 years which revolve round the work of Freud and the study of the unconscious and of the repressed unconscious, and this very interesting subject is therefore left where it was, with parents and educators still getting het up, knowing neither why the children lie nor why they are agin' it.

The book has no value, therefore, except as an illustration of the futility of writing on psychology in the second half of this century without an understanding of the unconscious.

Report of a Study Group on Paediatric Education. W.H.O. Technical Report Series No. 119. (Pp. 20. 1s. 9d.) London: H.M. Stationery Office; Geneva: World Health Organization. 1957.

The 13 members of the study group were convened from Europe, North and South America, India, Ceylon, the Philippines and Africa, and evidently found that the problems of undergraduate and postgraduate paediatric education were so diverse in their various countries that agreement could only be reached in broad generalizations. There are few detailed recommendations, although it was agreed that paediatrics could not be adequately covered in less than 300 hours, and that approximately one-quarter of the clinical period in the student curriculum should be devoted to this subject. The report may prove a help to those attempting to stake a claim for paediatrics as a new undergraduate and postgraduate discipline, but is too nebulous to advance materially paediatric education where this is already established.

Spastics in Cheyne Walk. Edited and compiled by JOAN SAUNDERS and MARJORIE NAPIER. (Pp. xiv+156; illustrated. 20s.) London: Pitman Medical Publishing Co. 1957.

This is an account of the successful struggle to organize a centre for spastic children in London, describing in considerable detail the planning and layout of this centre. As such it could be a helpful guide for the development of similar centres and will be read with interest by those associated with the care of spastic children. The nature of cerebral palsy and the work of the staff are explained in simple terms. The value of the staff reports and of the experience gained is as yet limited by the short time that the centre has been open.

International Congress of Gastroenterology. Fifth Meeting of l'Association des Sociétés Européennes e Mediterranéennes de Gastro-Enterologie, London, July, 1956. Edited by HAROLD EDWARDS. (Pp. 766.) Basel: Karger.

A large volume has been needed to reproduce the many papers read at this congress which was attended by distinguished visitors from almost all the European and Mediterranean countries, and many from the Commonwealth and the U.S.A.

Dr. Thomas Hunt, as president of the British Society of Gastroenterology, presided, and addresses of welcome were given by Sir Harry Platt and the Minister of Health.

Part one is mainly devoted to benign conditions of the oesophagus and contains much of paediatric importance. Of particular interest is a contribution by J. Nauta of Leyden describing fundamental research into the nature of the closing mechanism between oesophagus and stomach. He demonstrates that the closure is valve-like in nature due to the oblique inlet, and to the support of the diaphragm and oblique muscle fibres in the stomach wall: the actual watertight closure is insured by a rosette of gastric mucosal folds of which he provides endoscopic photographs. There are a number of papers on neuromuscular abnormalities and on various aspects of hiatus hernia, with excellent radiographic reproductions. R. H. R. Belsey gives an account of 27 cases of oesophageal obstruction in childhood, occurring as a complication of chronic reflux oesophagitis, and implies that these cases are a frequent result of paediatric neglect: 'paediatricians are not yet sufficiently aware of the importance of reflux oesophagitis in infancy as a cause of vomiting . . .' In fact, of course, reflux is an extremely common symptom, and its control an elementary detail in the technique of infant feeding. Oesophagitis and stricture formation is the exception rather than the rule whether a hernia is present or not. Even so, his case of advanced stenosis in which 'treatment for acidosis, cyclical vomiting, marasmus and anaemia, and hysteria having failed a barium examination was carried out for the first time aged 5', must make us more careful to investigate the regurgitating infant in whom there is any evidence of bleeding or dysphagia.

In the second part, consisting of short papers, there is an account of infantile cirrhosis of unknown aetiology from India by F. P. Antia and T. P. Bharadwaj and, also of special interest, a detailed account of the treatment of hepatic coma by dietary protein withdrawal and broad spectrum antibiotic therapy by Sheila Sherlock, W. H. J. Summerskill and A. M. Dawson. A review of work on coeliac disease is given by W. Sheldon who suggests that the role of gluten is sufficiently established to justify the use of the term gluten intolerance in preference to coeliac disease.

In part three ulcerative colitis is discussed in all its aspects. There is a discernible trend to early surgery while medical treatment of this strange illness remains so unsatisfactory, but a number of those contributing emphasize the psychosomatic aspect of the disease, and its probable origin in errors of emotional development in childhood.

Lehrbuch der Kinderchirurgie. By M. GROB, in collaboration with MARGRIT STOCKMANN and MARCEL BETTIX. (Pp. 775; 876 figures. DM 1570.—) Stuttgart: Georg Thieme. 1957.

Dr. Grob is to be congratulated on this splendid work, which apart from ear, nose and throat surgery, covers every aspect of paediatric surgery. The standard of the book throughout is so high that it is difficult to single out any section for special praise. The large section on chest surgery including cardiac surgery, and the beautifully illustrated chapters on abdominal and genito-urinary surgery are excellent, but perhaps the best chapters are the neurosurgical and orthopaedic ones. Dr. Grob is a distinguished plastic surgeon and he deals in masterly fashion with this speciality. The techniques and operations he describes are, however, largely unfamiliar to British and American surgeons.

In the preface the author hopes that the book will be of value to the paediatrician as well as to the paediatric surgeon. Perhaps the most interesting thing about this work is that the author is first and foremost a paediatrician and only incidentally a surgeon. The clinical descriptions of the various diseases and conditions aided by superb illustrations in black and white and in colour are outstanding.

The book is based on Dr. Grob's wide personal experience and as his practice varies in many ways from that generally adopted in the Anglo-Saxon countries, there is much that is interesting to the English speaking reader. Unfortunately there are hardly any references and it is not always clear whether Dr. Grob describes his own methods or those of other surgeons. The reader is often at a loss to decide who carried out all the original work, reference to which is made throughout. These remarks are not meant to detract from the value of Dr. Grob's original contributions to paediatric surgery, as for instance, his highly successful conservative treatment for exomphalos.

The book is most beautifully produced, paper, print and especially illustrations are all of very high quality. Unfortunately the price is extremely high.

VENO-OCCLUSIVE DISEASE OF THE LIVER AND INDIAN CHILDHOOD CIRRHOSIS

BY

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Cirrhosis of the liver is rare in childhood in the temperate zone and it is then usually due to some specific and traceable cause, such as Rhesus incompatibility, galactosaemia, congenital syphilis, in association with congenital abnormalities of the biliary apparatus, or following infective hepatitis. In most of the subtropics and tropics—at least according to present probably incomplete evidence—cirrhosis in childhood is somewhat more common, but it is still infrequently seen, despite the fact that the condition may have a high incidence amongst adults.

There appear to be only two widely separated regions of the world from which cirrhosis in childhood has been commonly reported in the medical literature—the West Indian island of Jamaica and the subcontinent of India, especially the eastern States of Madras and Bengal.

As it has recently been possible for the writers collaboratively to have had experience in both regions, the present paper has been written in order to compare clinical and histological features of cirrhosis in childhood as seen in both Jamaica and Calcutta, West Bengal.

VENO-OCCLUSIVE DISEASE OF THE LIVER

Awareness that cirrhosis was common enough to be a public health problem among Jamaican children in the lower socio-economic groups was initiated by the original clinical accounts of McFarlane and Branday (1945), Roys (1948) and Waterlow (1948).

The work of Hill, Rhodes, Stafford and Aub (1953) clarified the clinical picture, initiated the investigation of the histology and suggested possible aetiological factors. More recently, Bras, Jelliffe and Stuart (1954) demonstrated the predominant role of an obliterating process in the hepatic vein radicals in the morphogenesis, so that the condition was designated 'veno-occlusive disease of the liver' (V.O.D.).

Clinical Picture. The clinical picture has been described by Jelliffe, Bras and Stuart (1954a, 1954b), and may be summarized in the following three, often ill-defined, overlapping stages (Fig. 1): (1) Acute hepatomegaly (2 to 10 cm.) developed suddenly in five to 10 days, mainly in young children of from 18 months to 3 years of age, often with ascites, frequently after non-specific upper respiratory tract infection and often subsiding with or without treatment in four to six weeks. (2) Subacute, persistent, firm hepatomegaly, with or without recurrent ascites, may occur spontaneously or after the acute stage; it may subside clinically, with a high protein diet or pass into the chronic state (Fig. 2). (3) Chronic, the clinical picture of cirrhosis, is shown in Fig. 3.

Recently, veno-occlusive disease has been shown to occur, although less commonly, in Jamaican adults (Stuart and Bras, 1955), while it has also been discovered in another West Indian island, Barbados (Stuart and Bras, 1956).

Morbid Anatomy. The sequence of histological change, as demonstrated by both liver biopsies and necropsies, has been described by Bras *et al.* (1954), by Bras and Watler (1955) and more recently it has been summarized by Bras and Hill (1956).

The initial lesion in the acute stage is a subendothelial intimal thickening, with partial occlusion of the lumen, in small and medium sized branches of the hepatic vein, associated with centrilobular congestion. If the condition persists, atrophy and loss of liver cell cords occurs followed by a centrilobular (non-portal) fibrosis. The intimal thickening in later stages is composed of fibrous tissue. The liver in chronic cases is diffusely, finely granular and macroscopically indistinguishable from

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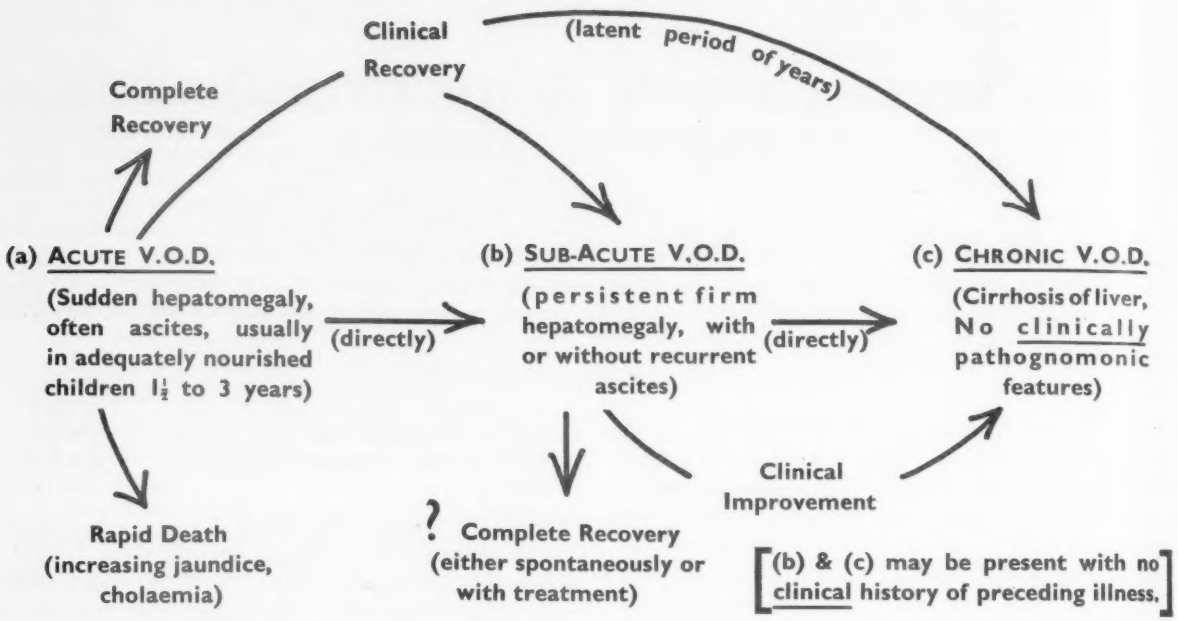
Clinical Recovery
(latent period of years)
Complete Recovery
(a) ACUTE V.O.D.
(Sudden hepatomegaly, often ascites, usually in adequately nourished children 1½ to 3 years)
(directly)
(b) SUB-ACUTE V.O.D.
(persistent firm hepatomegaly, with or without recurrent ascites)
(directly)
(c) CHRONIC V.O.D.
(Cirrhosis of liver, No clinically pathognomonic features)
Clinical Improvement
Rapid Death (increasing jaundice, cholaemia)
? Complete Recovery (either spontaneously or with treatment)
[(b) & (c) may be present with no clinical history of preceding illness.]

FIG. 1.—Diagram of the clinical natural history of veno-occlusive disease.

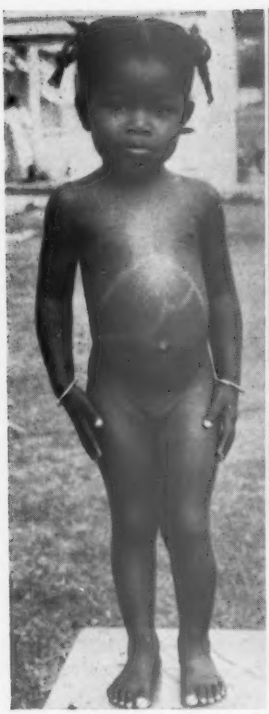

FIG. 2.

FIG. 3.

early Laennec's cirrhosis, although histologically the cirrhosis is clearly not portal.

Aetiology. It has been postulated tentatively that veno-occlusive disease in Jamaican children may be due to the effect of an as yet unidentified toxin on the liver of undernourished children. The nature of this toxin is unknown, but the frequent association of cases of acute veno-occlusive disease with preceding respiratory tract infections, including whooping cough, may be significant, while the practice of drinking over 200 different varieties of home-prepared herbal infusions, known as 'bush-teas', may also be relevant (Asprey and Thornton, 1953). The latter hypothesis has received support from the recent report of the condition in a cow in Jamaica (Bras and Berry, 1956), and direct attempts to reproduce the disease in experimental animals fed on bush-teas have supported this theory. Moreover, Selzer and Parker (1951) described an outbreak which began as acute Chiari's syndrome caused by eating bread made from inadequately winnowed

FIG. 2.—A Jamaican girl with subacute veno-occlusive disease showing symptomless hepatomegaly only.
FIG. 3.—Jamaican boy with chronic veno-occlusive disease showing the picture of fully developed cirrhosis.

wheat contaminated by a species of senecio, or ragwort, a common wild plant, while, even earlier, Davidson (1935) had demonstrated that retrosine, one of the alkaloids of senecio, produced an endothelial proliferation in the central and sublobular veins as its primary effect.

Recent studies (Bras, Berry and György, 1957) on experimental animals have shown that histological lesions identical to those of veno-occlusive disease can be reproduced in the livers of cattle and horses by feeding them with certain toxic plants.

INDIAN CHILDHOOD CIRRHOSIS

Since its original description as a clinical entity by Sen (1887), it has been recognized that cirrhosis of the liver in young children is a not uncommon condition in various parts of India, and a considerable, somewhat repetitive literature has grown up on the subject, almost entirely confined to Indian medical journals (Radakrishna Rao, 1934). An authoritative review of the present situation has been published recently by the Liver Diseases Sub-Committee of the Indian Council of Medical Research (I.C.M.R.) (1955).

Nomenclature

A variety of different names have been employed at different times by various authors, including biliary cirrhosis (Gibbons, 1888), infantile cirrhosis of the liver (Lahiri, 1936), hypertrophic or biliary cirrhosis (Brahmachari and Brahmachari, 1938) and subacute toxic cirrhosis of infants (Radhakrishna Rao, 1935). None of these seem entirely satisfactory and, as the disease appears to affect young children rather than infants exclusively, the non-committal term 'Indian childhood cirrhosis' (I.C.C.) will be used in the present account.

Present Cases

Diagnostic Criteria. Precise criteria for case selection were difficult to formulate. As the early symptoms are indeterminate and non-specific, children were selected initially by finding a firm or hard hepatomegaly, after exclusion as far as possible of other known causes of liver enlargement, such as kwashiorkor, malaria, kalar azar, infective hepatitis and congenital syphilis. Associated splenomegaly, the development of a collateral circulation, ascites and jaundice were regarded as corroborative evidence, but not necessary for diagnosis.

This classification is obviously unsatisfactory when it is recalled that knowledge of the pathology of Indian children is rudimentary, especially as post-mortem examinations are rarely performed. It is quite probable that there are as yet unrecognized causes of hepatomegaly in early childhood in India, as for example, visceral larva migrans due to ingestion of ova of the dog or cat roundworm (*Toxocara canis*, *T. cati*) (Beaver, Snyder, Carrera, Dent and Lafferty, 1952), or even perhaps as a result of the continuous transhepatic migration of larvae of *A. lumbricoides*, an almost universal parasite in children in some parts of India.

In the present series, liver biopsies were undertaken whenever possible, although this was often not feasible. Of the first 13 cases, nine were biopsied with a modified Vim-Silverman needle, and, of these, four showed no abnormality histologically and one demonstrated only moderate fatty change. All five of these children showed only a moderate, firm enlargement of the liver, with no corroborative evidence of cirrhosis. In view of these negative findings, together with the present somewhat controversial and uncertain evidence of any early or specific histological lesions in this condition, it was decided not to include these five cases and to select cases more rigidly in future.

The present series is, therefore, composed of 15 children seen at either the Out-patient Clinic of the Calcutta School of Tropical Medicine or at the Child Welfare Clinic of the All-India Institute of Hygiene and Public Health. They were admitted to hospital for full investigation whenever possible, but this was often not practicable as parents refused to allow their children to be admitted or beds were not available in the always busy and overcrowded ward.

Cases were only included if they showed the tentative diagnostic criteria of hepatomegaly, as previously described, together with at least one definite physical sign probably corroborative of cirrhosis, such as splenomegaly, dilated collateral circulation, ascites or jaundice, and/or histological evidence of hepatic fibrosis at liver biopsy or necropsy. It is realized that this classification is also open to criticism, especially as it excludes early cases about which very little is known.

Age Incidence. The average stated age at which children were brought to the clinic in the present small series was 3 years 5 months, with a range of from 11 months to 8 years 10 months. Apart from possible inaccuracies due to incorrect ages given by parents, it will be appreciated that this cannot be taken as an index of age of onset, as several children at least had previously attended other hospitals, private scientifically trained physicians or Ayurvedic healers.

Sex Incidence

As noted in the Indian Council of Medical Research report (1955), a number of workers have

remarked on a higher incidence in male children, while others found no difference in sex distribution (Achar and Raju, 1951, quoted by the Indian Council of Medical Research, 1955). In the present group, seven children were girls (47%), while the remainder (53%) were boys.

Family History. It has often been noted that more than one sibling in a family may be affected, and estimates of the frequency of familial incidence vary from about 20 to 40%. In the present group, only one child (7%) had a family history suggestive of fatal cirrhosis in an older sibling.

Signs and Symptoms. All patients had a slow and insidious onset, which is in agreement with the literature. In no instance was this abrupt as in acute veno-occlusive disease, and there was never any preceding history of jaundice. Parents of affected children reported that the illness had begun with the gradual onset, over periods varying from 4 months to 3 years, of the following clinical features: abdominal enlargement in two children (13%), general ill-health and lassitude in two (13%), vague upper abdominal discomfort in four (27%), poor appetite in five (33%), loss of weight in eight (54%), loose stools in six (40%) and dimness of vision in one child (7%).

Clinical examination revealed the following features in addition to a firm to hard hepatomegaly: splenic enlargement in eight children (54%), ascites, varying from just detectable to tense distension of the whole abdomen in eight (54%), a conspicuous collateral circulation in seven (47%), jaundice in eight (54%), clubbing of the fingers in two (13%) and oedema in one child (7%) (Figs. 4 and 5). In addition the following general features were noted: probable malnutrition (as evidenced by stunting, poor muscle tone) in six children (40%), obvious wasting of muscles and subcutaneous fat in six (40%), clinical anaemia in five (33%), rachitic stigmata in one (7%), follicular keratosis in two (13), Bitot's spots in one (7%) and bleeding gums in one child (7%).

Laboratory Data. The following average results were obtained for the 11 children who were admitted to hospital: Haemoglobin 9·3 g. per 100 ml. (range 6·9 to 11·6); blood films for malarial parasites negative in all cases; Rhesus factor positive in five children tested; Wassermann reaction negative in all cases. A white blood count gave 11,000 per c.mm. (range 8 to 16,000), neutrophils 64% (range 50 to 74%); plasma proteins (total) 6·0 g. per 100 ml. (range 4·5 to 7·5); albumin 2·8 g. per 100 ml. (range 1·8 to 3·8), globulin 4·0 g. per 100 ml. (range 2·0 to 5·2). The following liver function tests were carried out: serum bilirubin, thymol turbidity, alkaline phosphatase, gamma globulin, serum cholinesterase. Abnormal results were found in at least one of these in each case, but no definite pattern emerged, except that advanced cases showed a definitely raised serum bilirubin level.

Helminth ova were present in the stools of nine children (hookworm four, roundworm three and both, two).

FIG. 5.

FIG. 4.—Indian cirrhosis of childhood in a Bengali girl, early in the stage of clinical cirrhosis, showing hepatomegaly, dilated collateral circulation and splenomegaly.

FIG. 5.—Indian cirrhosis of childhood in a Bengali girl late in the stage of clinical cirrhosis showing cachexia, hard hepatomegaly, ascites, marked collateral circulation and splenomegaly.

Course. The 11 children admitted to the ward were treated with a high-protein-high-vitamin diet, with added polyvitamin capsules. Associated infections were dealt with, if present, and ascites tapped, if needed. No other specific treatment was attempted.

The following results were obtained with treatment periods of from four to 10 weeks in these 11 clear-cut cases of cirrhosis: slightly improved generally (with no obvious effect on hepatic condition (four), no change (one), deterioration and taken home (three), died in hospital (three) (two in cholaemia and one with bronchopneumonia). Cases could not be followed up in the Out-patient Department or at home.

Socio-economic Background. This was considered as follows:

(1) PLACE OF RESIDENCE. According to the parents, the majority (66·6%) of the children had always lived in Calcutta City. Of the other five, three lived in adjacent rural West Bengal, while two had recently come from Amritsar, East Punjab, and Lucknow, Uttar Pradesh, respectively.

(2) RELIGION AND CASTE. Twelve of the 15 children (80%) were Hindus, while two were Muslims and one was a Sikh. Of the Hindus, four were Brahmins and the remaining eight were of non-Brahmin castes.

(3) ECONOMIC STATUS. This was very difficult to ascertain with any precision and even harder to define. However, three came of what can be called 'lower middle class' families, that is, with fathers working as clerks, small shop owners, etc. The majority were from lower socio-economic groups, such as vegetable sellers, unemployed, *bidi* (local cigarette makers), doorkeepers, etc. None, it must be stressed, came from the most abjectly impoverished *bustee* (slum) dwellers.

(4) DIET. Dietetic histories varied greatly and were never obtained with any degree of accuracy. Affected children were usually being fed on breast milk (up to about 2 to 3 years), a very little diluted cow's milk, some rice or barley, *dhal* (legumes) and occasionally fish. Older children were receiving some of the family *masala* (curry sauce). Depending upon the parents' financial status, goat's milk or dried powdered milk might also be added, although sometimes all milk might have been stopped in a mistaken attempt at dietetic treatment. Basically, then, the diet consisted of small quantities of milk together with mainly carbohydrate foods.

(5) TOXIC FACTORS. Enquiries were made to ascertain if any of the children had been receiving possibly toxic herbal remedies, and the use of Ayurvedic* medicines before the illness was admitted by six parents (40%), although no child was reported to have been given castor oil. Antecedent febrile illnesses were inquired about, in view of the possibility of the toxin of an infectious disease being aetiologically involved. In only one child was there a history of 'measles' just before the probable date of onset of the hepatic disorder.

Morbid Anatomy. Histological examination was undertaken in six of the total of 15 cases, four by liver biopsy and two following 'local' post-mortem examinations.

Results are summarized in the Table, and, as will be noted, the histology was similar to that seen in chronic veno-occlusive disease in all cases, especially in Nos. 3 to 6.

TABLE

SUMMARY OF MAIN HISTOLOGICAL FINDINGS IN SIX CASES OF INDIAN CHILDHOOD CIRRHOSIS

Case No.	Source	Main Histological Findings
XS/55/54	Needle biopsy	Advanced cirrhosis involving portal triads and branches of hepatic veins.
XS/55/149	Needle biopsy	Advanced cirrhosis, apparently involving portal triads and branches of hepatic veins.
XS/55/150	Needle biopsy	Marked fibrosis showing veno-occlusion of branches of hepatic veins.
XS/55/151	Needle biopsy	Fibrosis, apparently involving branches of hepatic veins.
XS/56/103*	Necropsy	Advanced cirrhosis with marked veno-occlusion of branches of hepatic veins.
XS/56/236	Necropsy	Fibrosis mainly centrilobular and involving hepatic veins with thickened walls.

* Case of Manik Das—full details given in text.

Typical Case Summary

Clinical History. Manik Das (XS/55/54), a Bengali boy, aged 3 years 9 months, was admitted with an eight-month history of the gradual onset of abdominal swelling, 'low fever' and general ill health. He had always lived in Calcutta and was a Hindu of the Sudra caste. The boy's father owned a small shop, allegedly earning R.150 (£11.5 or $32.20) monthly. There was no history of antecedent illness, and no Ayurvedic medicines or other herbals were stated to have been given. There had been two female siblings: one, aged 7 years, was alive and well, while the other was reported to have died six years previously of 'liver' when aged 4 years. Details of the past diet could not be obtained. The present diet consisted of a little breast milk, cow's milk ½ seer

* Ayurveda ('health from the Vedas') is the traditional indigenous system of medicine employed in India. A wide variety of predominantly herbal remedies are used.

(16 ounces) daily, together with a little barley, rice and fish occasionally.

Examination showed a thin, chronically ill boy with ascites, moderate jaundice and some dilated veins running upwards across the epigastrium. The liver was enlarged 5 cm. below the costal margin, and was hard and not grossly irregular. There was no clubbing. The spleen was enlarged 2 cm. Follicular keratosis was present on the elbows, while the tongue showed superficial ulceration.

Laboratory Investigations. Haemoglobin was 9·3 g. per 100 ml.; the white blood count 13,000 per c.mm. (neutrophils 58%, lymphocytes 37%). The Wassermann reaction was negative. Plasma proteins were 4·5 g. per 100 ml. (albumin 1·5, globulin 3·0). A blood film for malaria parasites was negative. The child was Rh positive. The stools showed no ova or parasites.

Course. The subsequent course in hospital was rapidly downhill and the child died 10 days after admission. Permission for a partial necropsy was obtained.

Necropsy Findings. The peritoneal cavity was found to be filled with slightly bile-stained fluid, and the whole liver was removed. The liver was finely nodular over the entire surface (Fig. 6) and the cut section showed fibrous septa and was slightly greenish.

The histological examination showed advanced cirrhosis with much fibrosis present in the form of septa causing pseudo-lobulation, but also there was a considerable increase of connective tissue inside the pseudo-lobules; while, in addition, there were further dense areas of fibrosis throughout the liver. The dense areas of fibrosis and the fibrous septa included portal triads as well as hepatic veins. The pseudo-lobules showed regeneration of liver cells as evidenced by liver cell cords of two or more cell layers in thickness.

There was much eosinophilic degeneration of the cytoplasm of the liver cells, many of which were seen to be disintegrating and polymorphonuclear leucocytes in varying number were present in such areas (Fig. 7). The liver cell nuclei showed polyploidy. The larger bile ducts in the portal triads were unaffected, while there was much proliferation of smaller bile ducts in the liver lobules in the areas of fibrosis. Some of these proliferated bile ducts contained bile. The interstitial tissue showed many cells, mainly polymorphonuclear leucocytes and lymphocytes (Fig. 8). The bile capillaries between the liver cells were clearly visible and occasionally markedly dilated.

The hepatic artery and portal veins showed no changes, but many of the hepatic veins were partially or completely occluded by subendothelial connective tissue formation (Figs. 9, 10, 11).

In comparing the appearance with chronic veno-occlusive disease, it can be said that the hepatic venous occlusion is about equal in extent, but that in chronic condition in Jamaica there is usually less involvement of the portal tracts. The histological picture, such as found in Fig. 12, obtained from a case of chronic veno-occlusive disease in a Jamaican child, and leaving many portal tracts free, cannot be matched in this liver. In veno-occlusive disease there is no marked bile duct proliferation such as here, while inflammatory cells are not pronounced. This condition, as initially described by Gibbons (1888), was indeed marked in this case.

Comparison with Cases Reported in the Literature

Onset. As noted earlier, all 15 cases in the present small series gave a history of gradual, insidious onset and progressive course, and this is in agreement with all previous accounts, although it is of interest to note that Achar and Chacko (1954) found that a quarter of a large group of cases in Madras were preceded by an attack of jaundice.

It is difficult to compare ages of the present cases with other reports, as it is sometimes not clear whether the ages recorded refer to the onset of symptoms or to attendance at hospital, quite apart from such well-known difficulties as inaccuracies and approximations in the figures given by the parents. However, according to the I.C.M.R. report (1955), the majority of reported cases have been between 1 and 3 years of age, so that the present group seem to be somewhat older than is usual.

Signs and Symptoms. In the literature cirrhosis in Indian children is classically considered as having three clinical stages: (1) Early (or stage of onset), (2) intermediate, (3) late. These have been termed precirrhotic, compensated and decompensated cirrhosis by Chatterjee (1940).

For the first or early stage, descriptions are extremely vague and non-committal, and vary considerably according to different authorities. Clinical features considered to be attributable to this stage of the disease are such protean ones as general ill-health and lassitude, altered appetite (either anorexia or increased), constipation or diarrhoea, low or occasional fever, flatulence and minor abdominal distension. According to some, the liver is just palpable, while the stools may be pale.

In the second or intermediate stage, children are alleged to be peevish and irritable, and to have protuberant abdomens, livers definitely enlarged with a sharp, 'leafy' edge, together with some splenomegaly and dilated superficial abdominal veins. Ascites and some ankle oedema may be present, while the sclera are subicteric and the stools pale.

In the third or final stage, the picture is that of clinically obvious cirrhosis. The child is wasted, usually icteric and with a prominent abdomen, due

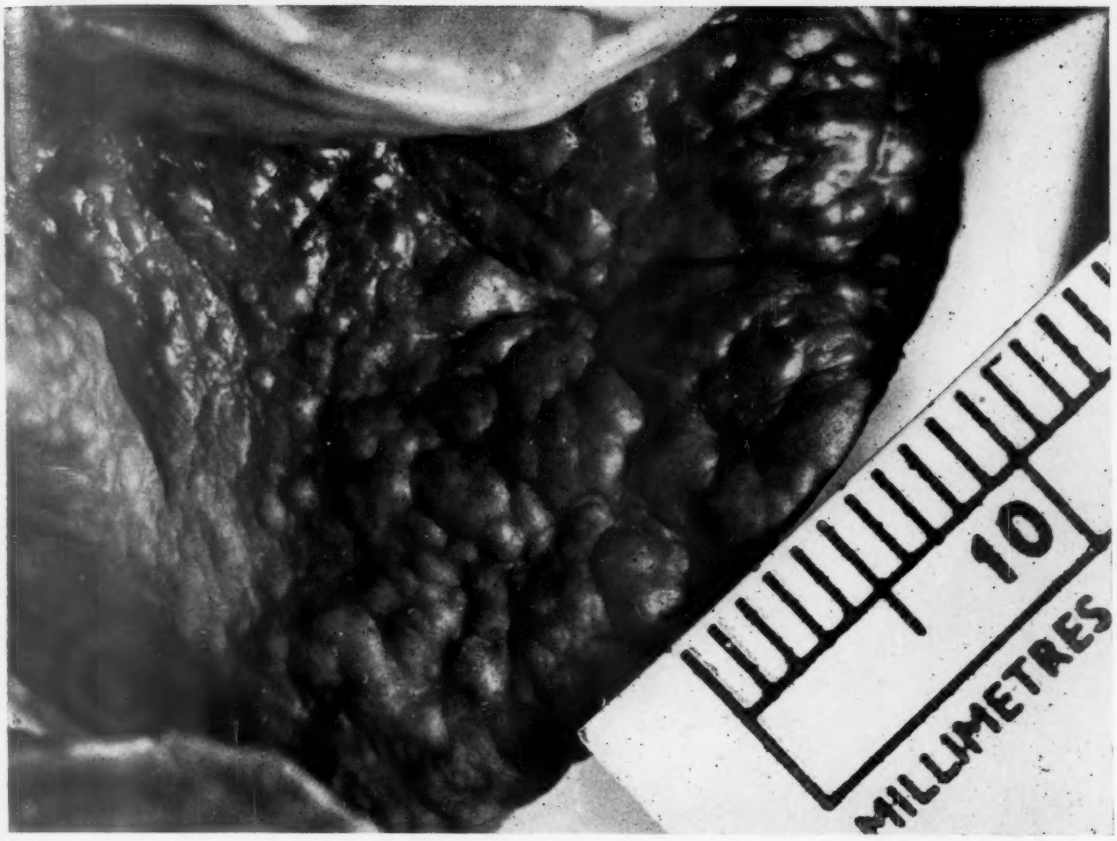

FIG. 6.—Picture of liver at necropsy in a case of Indian cirrhosis of childhood showing a finely nodular surface (Manik Das).

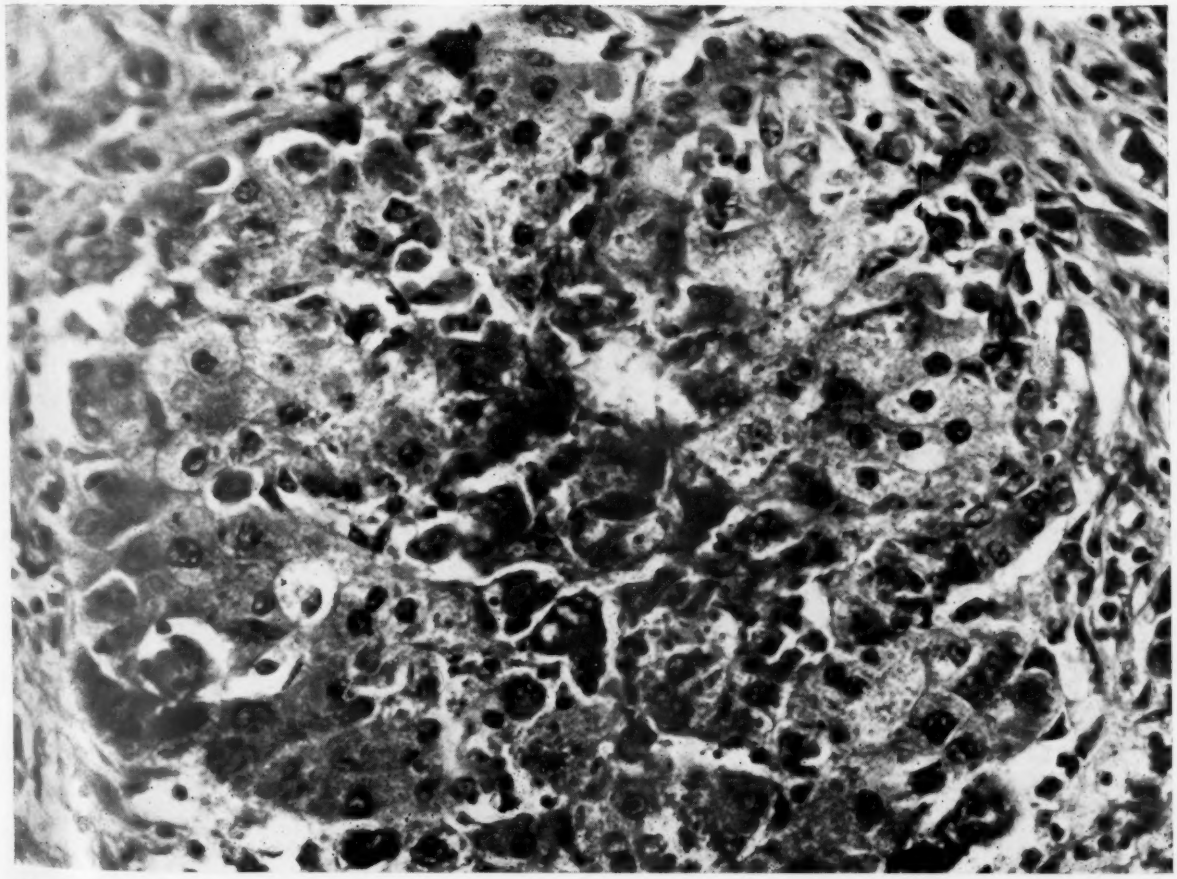

FIG. 7.—Nodule of regenerated liver cells, with many cells visible in the centre undergoing eosinophilic degeneration with necrosis (Case of Manik Das). Haematoxylin and eosin × 340.

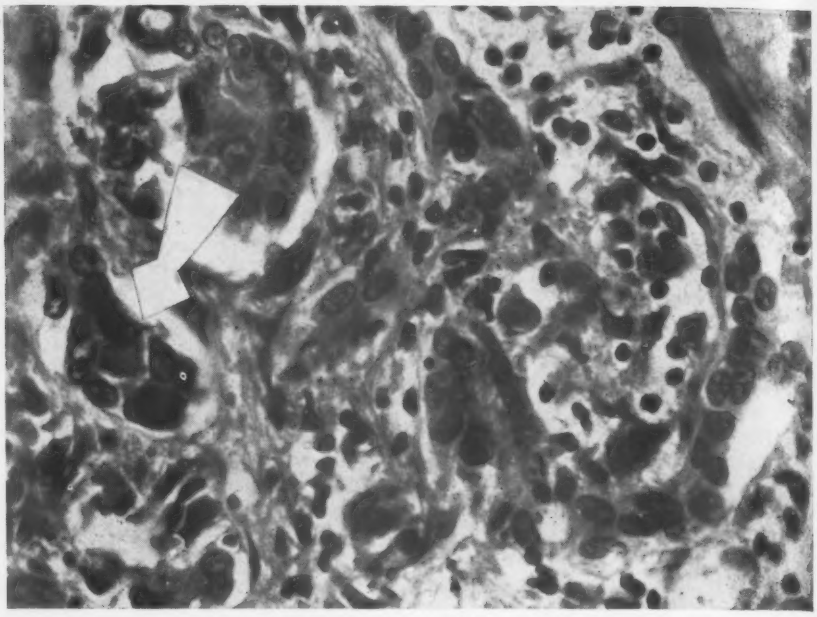

FIG. 8.—Liver showing bile duct proliferation with 'thrombus' in the bile duct at arrow, and marked infiltration with polymorphonuclear leucocytes and lymphocytes in the intestinal tissues (Manik Das). Haematoxylin and eosin × 450.

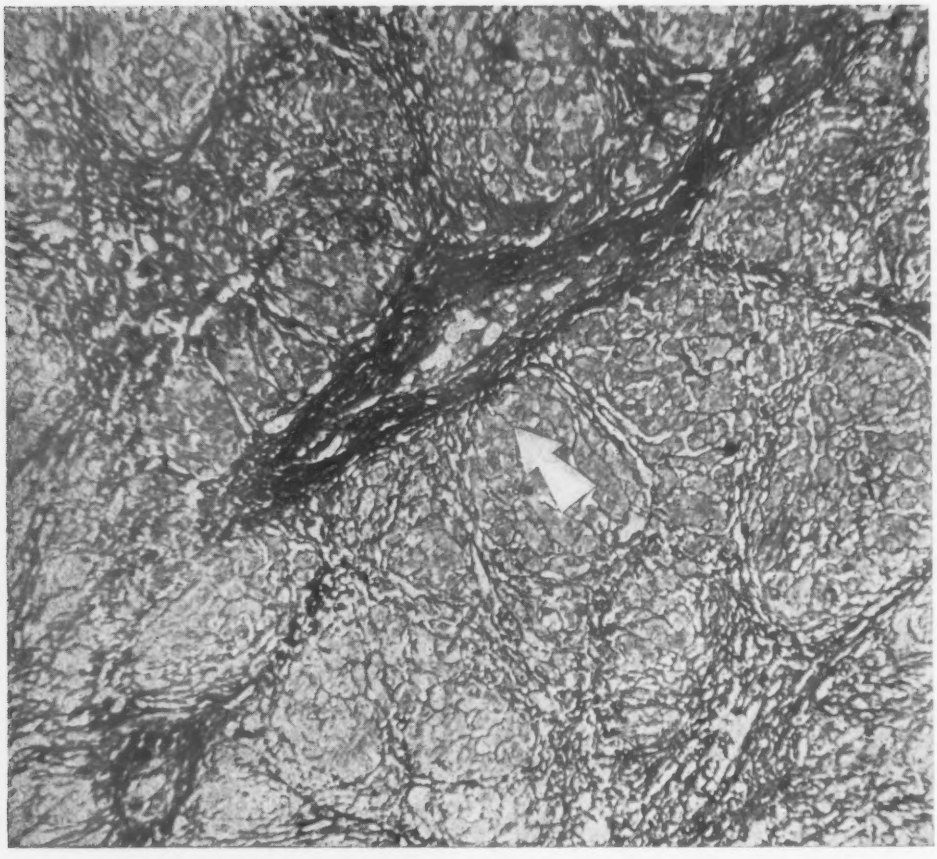

FIG. 9.—Occlusion of branches of the hepatic vein (Manik Das). Reticulin × 60.

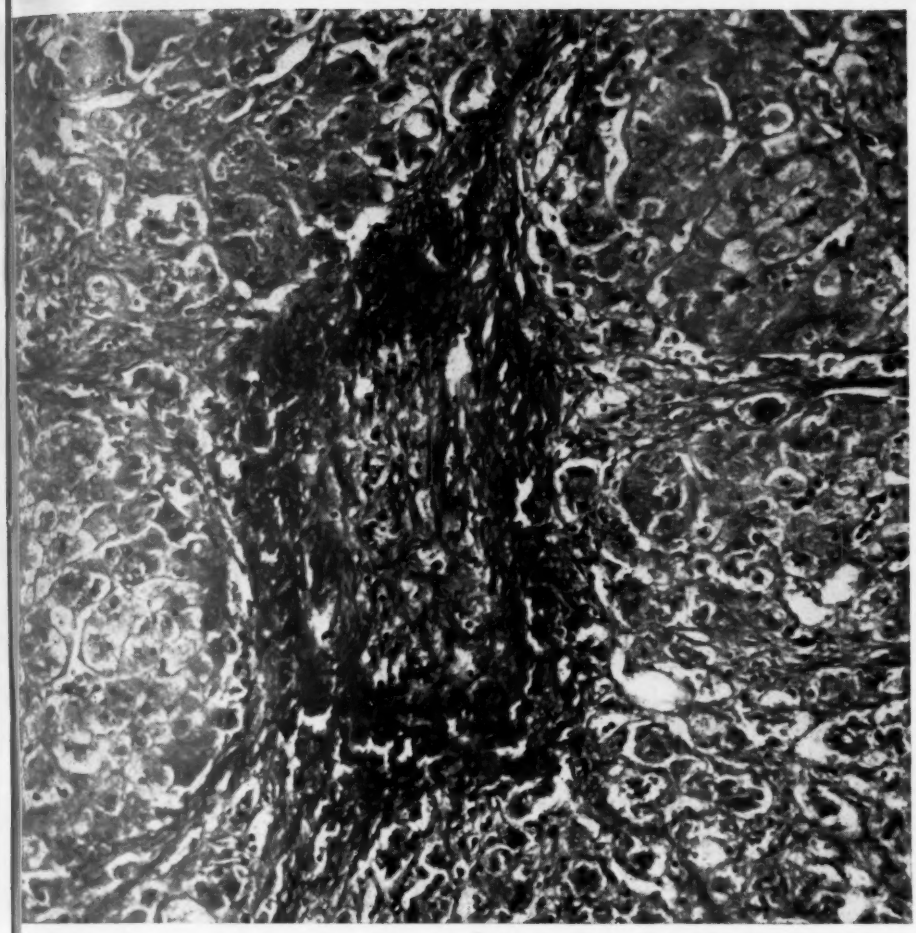

FIG. 10.—Liver showing almost complete occlusion of a branch of the hepatic vein (Manik Das).

FIG. 11.—Occluded branch of the hepatic vein, showing small blood vessels (? recanalization) (Manik Das). Mallory trichome × 170.

FIG. 10.

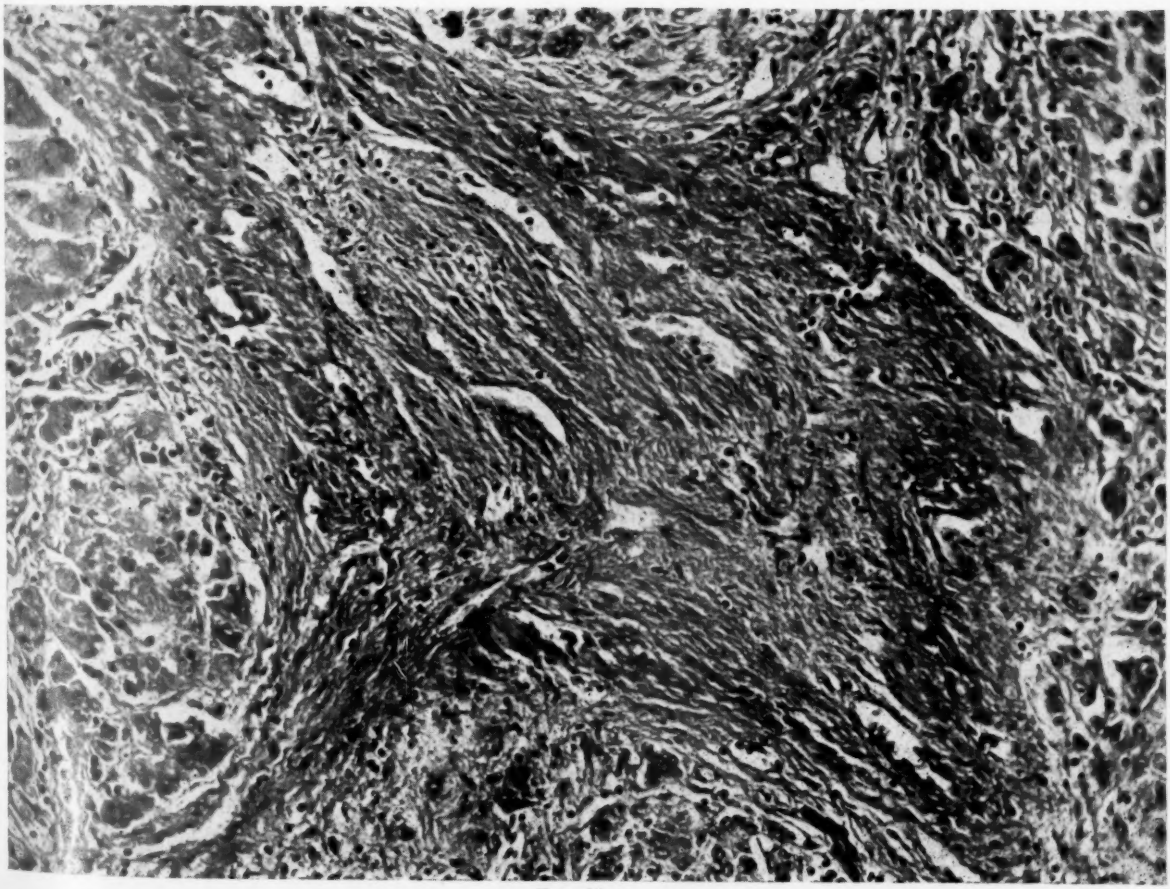

FIG. 11.

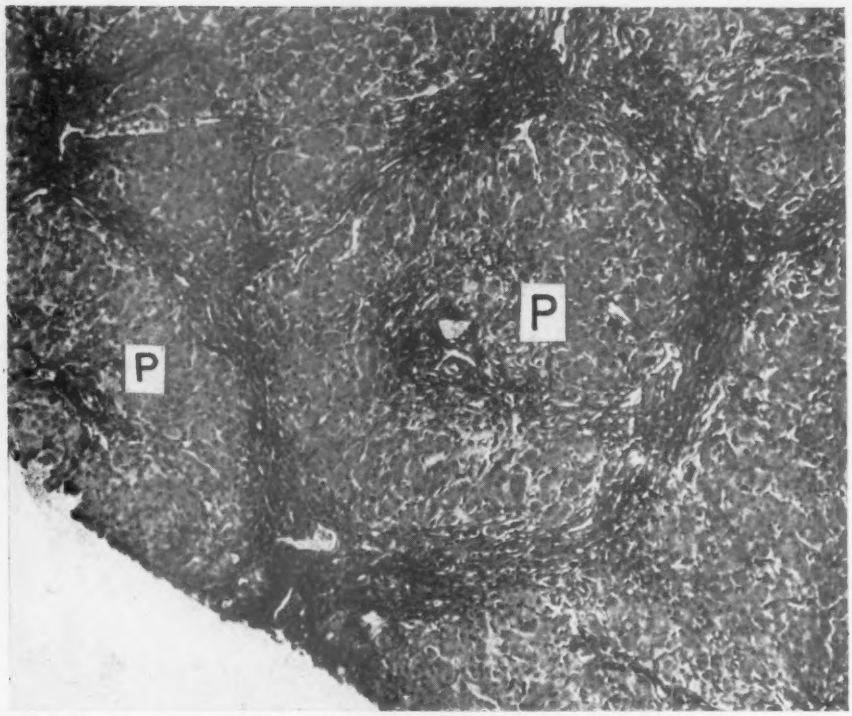

FIG. 12.—Jamaican child with chronic V.O.D. in whom the liver showed non-portal cirrhosis.

to ascites, smooth or finely irregular, hard hepatomegaly and, usually, definite splenomegaly. Marked engorgement of the collateral circulation will be visible. The urine will be scanty, and may contain albumin, bile pigments and salts.

TWO-STAGE CLASSIFICATION. In view of the apparent present confusion and lack of specificity of alleged early features (*i.e.*, general ill-health, flatulence, pale-coloured stools, etc.), many of which can be seen in a percentage of Indian children attending paediatric out-patient or child welfare clinics, the following 'two-stage' classification is suggested tentatively as a practical, more easily definable and standardized system of identification, at least until further knowledge of the natural history of the disease is acquired. It must be stressed that these two stages overlap and merge into one another.

(i) *Stage of Hepatomegaly*. It is generally agreed that the most suggestive clinical sign, both early and late, is a firm or hard, painless enlargement of the liver, coming on insidiously, and in India, young children, especially in the first five years of life, should be suspected of having early cirrhosis, if other causes of hepatic enlargement—such as malaria, kala azar, kwashiorkor, congenital syphilis and congenital lesions of the bile ducts—can be excluded. (It is realized that at present there is no proof that all cases pass through a stage of hepatomegaly early in their evolution to frank cirrhosis. Nevertheless, this concept of a stage of hepatomegaly, based on the consensus of practical experience and clinical evidence, may be used at least temporarily until the acquisition of newer knowledge permits of more specific diagnostic criteria.)

In addition, the physiologically palpable soft liver found in many young children in the first few years of life, especially if exaggerated by chest deformities such as occur in rickets, will have to be borne in mind as will the transient soft hepatomegaly which is considered by some to occur as a temporary phenomenon in young children during any acute febrile illness. The acute tender liver of amoebic hepatic involvement can be mentioned, but should present no diagnostic problem.

The diagnosis of probable early I.C.C. depends, therefore, as judged by present knowledge, simply on finding a definite firm or hard hepatomegaly for which no other explanation can be discovered. Other variable and apparently entirely non-specific features may be present, such as general ill-health, low fever, etc. Chaudhuri (1944) says that there may be complaints of a general nature vaguely referable to the digestive system.

Clinical diagnosis at this stage can only be presumptive until the development months later of definite cirrhotic features. A positive family history

is suggestive, but gives no scientific proof. Specific laboratory biochemical tests do not at present exist. Liver biopsy would appear ultimately to offer the best possibility of early diagnosis, but much further work is needed to investigate the histopathology of what may well be a heterogenous group and especially to delineate the specific changes of early I.C.C.—a difficulty increased by present incomplete knowledge of the morbid anatomy of the liver of normal, but undernourished, Indian children. In the specimens discussed in the I.C.M.R. report (1955), initial changes consisted of patchy, but fairly widespread, degeneration of liver cells, associated with mild reactive change in and around Glisson's capsule and in the sinusoids. However, as this Committee themselves imply, these findings cannot be accepted as universally applicable as definite histological criteria suitable for use in early diagnosis.

The difficulty of making a diagnosis on clinical grounds alone is clearly shown, when, in the early stages of the present investigation, five children with moderate firm hepatomegaly were found, at least in the small fragment of liver available following needle biopsy, to have apparently normal histology (four) and moderate fatty change (one). Similarly, as noted in the I.C.M.R. Report (1955), a number of children in Achar's large-scale investigation in Madras in South India were found to show no abnormality at liver biopsy, despite their having what were considered to be abnormal palpable livers.

(ii) *Stage of Clinical Cirrhosis.* At this stage, a diagnosis is usually relatively simple on clinical grounds. All the children in the present small series of 15 fell into this category. Affected children show a hard, smooth or finely granular enlargement of the liver, together with some or all of the following features of hepatic disease: ascites, icterus, splenomegaly, dilated collateral circulation. Loss of weight and anaemia are usual. Ankle oedema is not uncommon. The stools are clay-coloured and the urine is dark, containing bile pigments and salts, and, occasionally, albumin. Moderate intermittent fever is usual. Laboratory tests have not been sufficiently investigated, but a raised serum bilirubin level, some degree of anaemia and a variable pattern of abnormal liver function tests are seen. Leucocytosis is often present, but may well be rather related to intercurrent infection, especially of the respiratory tract. The histology of the liver, as shown by biopsy and at necropsy, is that of a diffuse fibrosis, details of which will be given later.

As to differential diagnosis, other forms of cirrhosis must be excluded, including those associated with congenital syphilis, Rhesus incompatibility, post-hepatitic scarring, and, in young infants, congenital atresia of the bile ducts. These can usually be excluded by the history and laboratory investigations.

In West Bengal, Cooley's anaemia presenting with jaundice and hepato-splenomegaly can be differentiated by the marked anaemia, characteristic skull shape, and other haematological investigations.

Socio-economic Background. This was considered under specific headings:

(1) Geographical Incidence. According to the available medical literature, I.C.C. has only been reported from India, with the exception of the few cases described from Colombo, Ceylon, by Karunaratne (1951) and by Fernando (1954). Within India, the disease has been reported from all States, with the apparent exceptions of the East Punjab and Pepsu. The condition has always been most commonly recorded in Madras and West Bengal, especially Calcutta. It is of interest—and may be of aetiological significance—that this type of childhood cirrhosis does not seem to have been described from other parts of south-east Asia.

Information regarding the public health significance of I.C.C. is meagre. No statistics are available summarizing the incidence of the disease in the population as a whole in any part of the country. As the I.C.M.R. report (1955) observes, most series have been from quite unrepresentative population samples, that is, from hospitals in large towns. There appears at the moment to be an impression amongst some experienced clinicians in larger Indian cities that the condition is seen less frequently nowadays than it was 15 years ago.

(2) Religion and Caste. As has been stressed by all observers, the disease occurs most commonly in Hindus, often of the Brahmin caste. However, it must be realized that Hindus form the vast majority in most areas of India. That I.C.C. occurs amongst non-Brahmins is clearly shown by even the present small series where eight were so classified. Similarly other workers have shown that the condition does affect Muslims, Anglo-Indians and other minority groups. The I.C.M.R. (1955) summarizes the situation accurately when it says: 'It is impossible to say on the basis of available information whether the observed predominance among the Hindus is merely a reflection of their numerical superiority in the country or whether they are more susceptible to the disease than others.'

(3) Economic Status. It has long been remarked that I.C.C. does not primarily affect the very lowest

and most impoverished socio-economic groups, as does kwashiorkor, for example. As Prabhu (1940) rightly observes: 'Curiously enough, the poorest classes seem to be exempt from it. It is hardly ever found among sweepers, rickshaw-pullers, labourers or in vagrant classes or in slum areas, among whom diseases attributable to malnutrition are found.'

While this was certainly so in the present small series, as the I.C.M.R. (1955) report stresses, this does not necessarily mean that malnutrition plays no part in the aetiology, 'for it is well known that the diet of some of the middle and even upper classes may be unbalanced and qualitatively unsound, although quantitatively adequate'. (In Calcutta this was certainly observed to be correct in another context, in that rickets was found to occur much more commonly amongst the children of strictly vegetarian Marwari merchants of considerable wealth.)

Morbid Anatomy. Despite the recent increased interest in the pathology of I.C.C. and the consequent intensification of active research, comparatively few necropsies have been reported, probably not more than 40 in all, and these have all been in advanced cases dying in the final phases of the stage of clinical cirrhosis. Thus, Bhende and Deoras (1954) stress that the records of only nine necropsies were available to them from the period 1926 to 1954, in the archives of a leading hospital in Madras.

All accounts are in general agreement as to the gross appearance of the liver in advanced cases that come to necropsy.

> 'The organ is usually shrunken, stained green with bile, of normal shape with sharp margins and firm consistency. The capsule is thick and somewhat opaque white in colour and free from adhesions or exudation. The capsular surface may be either smooth with indistinct lobular markings, or may be uneven, granular or flatly nodular, particularly on the under-surface. The sectioned surface is greenish in colour with obliteration of the normal lobular pattern by a diffuse fibrosis. It presents either a smooth greyish-green surface finely mottled with small scattered dark-green areas or a finely granular surface with a diffusely spread greyish-green fibrous network enclosing small rounded islands of regenerating parenchyma' (I.C.M.R., 1955).

Gibbons (1888) compared the bile-stained areas of regenerating hepatic tissue to 'mustard seed granules'; while the surface of the liver has been considered to have a 'morocco leather' appearance.

Findings at the two partial necropsies in the present series agreed completely with this general naked-eye description. A comparison of the histological changes found at necropsy and at liver biopsy in the present cases and by other workers is made later in this paper, when these are also compared with the morbid anatomical findings of veno-occlusive disease in Jamaican children.

Treatment and Course. There is general agreement that the prognosis of I.C.C., in what has here been termed the stage of clinical cirrhosis, is usually hopeless, in that, after a period of months, or even a few years, deterioration occurs and death results from cholaemia, secondary infection, or, less commonly, oesophageal haemorrhage. The situation does not seem to have altered since 1890 when Sen (quoted by Krishna Rao, 1950) noted that the established disease was 'more certain of its victims than the dreaded cholera or smallpox'.

A large number of different, often bizarre forms of treatment, usually based on a particular worker's theoretical concept of the aetiology, have been tried at various times and cures claimed. Inspection of such claims invariably shows a lack of precise criteria for initial diagnosis, absence of control cases, inadequate follow-up and small numbers of cases. Many children allegedly cured may not have been suffering from the condition at all. The I.C.M.R. report again accurately summarizes the situation: 'No convincing evidence has so far been produced to show that the natural course of the disease is in any way modified by the several régimes which have been advocated enthusiastically from time to time.'

One difficulty, at least in West Bengal amongst 'lower middle class' parents, is the fact that there is a wide awareness of cirrhosis as a serious, often fatal childhood disease—often known locally by the English word 'liver'. The anxiety of parents of this type provides a fertile field for quacks and for widely advertised proprietary and Ayurvedic 'liver cures', such as those containing extract of Kalmej (*Andrographus paniculata*).

Not infrequently 'liver' is diagnosed in Bengali children on the basis of such common and non-specific features as lassitude, fairly loose, rather pale stools and slight fever, together with physiologically palpable liver in a flabby, somewhat anaemic child.

In view of the present ignorance of the cause of I.C.C., therapy is empirical with a high-protein, high-vitamin diet, together with plenty of added sugar and supplementary polyvitamins, and the treatment of associated infection. Terminally, protein should be reduced, in view of the known toxic effect on the central nervous system in cases of liver damage of protein breakdown products (Sherlock, Summerskill, White and Phear, 1954).

When considering the present-day treatment of I.C.C., and especially some of the complex régimes that have from time to time been advocated, it is

perhaps salutary to consider the original form of therapy advocated by Sen (1887): 'Muriate of ammonia, iodide of potassium, nitro-hydrochloric acid, taraxacum, ipecacuanha and rhubarb in a mild bitter infusion were administered internally, while small mustard plasters, iodine ointment, tincture of iodine and nitro-hydrochloric acid baths were used externally.'

INDIAN CHILDHOOD CIRRHOSIS AND VENO-OCCLUSIVE DISEASE OF THE LIVER COMPARED

Clinical Picture

The clinical picture of veno-occlusive disease of the liver as seen in Jamaican children and that of Indian childhood cirrhosis present many similarities and certain apparent differences.

Economic Status

In both conditions, affected children do not come from the very lowest socio-economic groups. However, in India, it is well known that cases also occur in 'upper middle class' families as, for example, where the father is a physician or merchant. This is unknown in Jamaica.

Diet and Nutrition

Apart from the study by Rhodes (1952) in Jamaica, when she found that affected children were having a diet low in protein, detailed dietetic investigations do not appear to have been carried out on either group. However, in both conditions it is probable that the diet is usually inadequate, and that this is reflected in the children's nutritional status. In the early stages of both diseases, children are usually undernourished without showing evidence of gross malnutrition, while in the final cirrhotic stage, cachexia develops as a result of the chronic illness.

Onset and Clinical Features

Jamaican children first presenting with either the subacute or chronic stages of veno-occlusive disease very much resemble the usual picture of I.C.C. They are usually brought in by parents with complaints of abdominal swelling, due to ascites and/or an enlarged liver. Following this, both groups show the same progressive downhill course over months or years, sometimes with long clinically latent periods, but eventually terminating fatally in cholaemia, oesophageal haemorrhage or intercurrent infection.

Personal experience and descriptions in the medical literature give the impression that both early marked dilatation of the collateral circulation and haemorrhage from oesophageal varices are commoner in veno-occlusive disease, while jaundice seems to occur earlier and in a higher percentage. In addition, Indian children with childhood cirrhosis are reported to show more general features of ill-health, such as loose stools, poor appetite, etc.

An important difference between veno-occlusive disease in Jamaica and I.C.C. is that cases of the former may present as acute veno-occlusive disease, that is, with an initial acute episode of hepatomegaly and ascites, during which the histological picture of acute exudative subendothelial thickening of small and medium sized branches of the hepatic veins can be found in liver biopsy material. In addition, a number of cases of veno-occlusive disease presenting in the subacute or chronic stage have a past history suggestive of a possible acute episode of hepatic veno-occlusion. As far as can be discovered by perusal of the literature, by discussion with experienced clinicians and as a result of personal observation, this type of initial acute episode has never been reported from India.

If the ages of onset of cases of Jamaican veno-occlusive disease presenting in the subacute or chronic stages are compared with the present series, it will be seen that the range is very similar, that is, from about 1 to 9 years. However, in most accounts of I.C.C. the main incidence is given as between 1 and 3 years, so that most evidence points towards the Indian variety of cirrhosis usually manifesting itself some two or three years earlier than is customary in Jamaican cases. Finally, as a point of similarity, both conditions may often show a familial incidence.

TROPICAL CHILDHOOD CIRRHOSIS IN OTHER AREAS

Although not as commonly reported, nor, apparently, such a public health problem as in Jamaica and India, cirrhosis of childhood has also been the subject of investigation in certain other tropical regions.

In Egypt, where cirrhosis in children and adults is usually considered to be mainly the result of combined malnutrition and schistosomiasis, Hashem (1948) has also described what he terms 'a variant of subacute portal cirrhosis encountered in Egyptian children', which is unrelated to bilharzial infection. This condition, which occurs mainly in children between the ages of 8 months and 7 years, is of unknown aetiology. The main clinical features appear to be the fairly rapid onset of cirrhosis, with a very enlarged, firm liver and dilated, tortuous thoraco-abdominal veins. Oedema of the lower limbs is a frequent finding, and the spleen is enlarged

in one-third of cases. Haematemesis is not reported. The syndrome is of especial interest as, as will be noted later, the liver histology very much resembles that of veno-occlusive disease.

Walters and Waterlow (1954) have reported an important and broad-based investigation into the pathogenesis of hepatic fibrosis in African children and young adults in the Gambia. In these cases, the main features appear to be general ill health, distended abdomens and ascites. Jaundice was unusual, and dilated collateral circulation and haematemesis were not noted. Anaemia was often a conspicuous feature. No history of previous acute episodes was mentioned.

HISTOLOGICAL FINDINGS

Radhakrishna Rao (1935, 1954) described histological studies in I.C.C. when widespread obliterative lesions of the smaller divisions of the hepatic venous tree were found and appeared to be playing an important part in the evolution of the cirrhosis. Of the many articles from India, it has become evident that histological study of I.C.C. has been relatively limited because of the difficulty of obtaining necropsy and other material. Bhende and Deoras (1954) summarized the various reports on the pathological findings as follows. Necrosis of liver cells uniformly distributed throughout the organ, but varying in degree in different areas, has been observed by most writers. Fibrous bands, as well as diffuse fibrosis throughout the liver, have been reported; this fibrosis includes portal triads, but, according to some writers, may also originate from and include branches of the hepatic vein which may or may not show thickening of their walls and/or obliteration of their lumina. Dr. Y. M. Bhende of Madras has kindly allowed us to study again the histology of seven of his cases and we confirm his findings that, in several of the sections, there is very marked obliteration of the hepatic veins (Figs. 13, 14). It should be noted that, in the paper by Bhende and Deoras (1954), the nine cases examined histologically represent hospital necropsy material collected over a period of 25 years and it must have been difficult to establish that these children did, in fact, all belong to the same clinical entity. On the whole, authors other than Radhakrishna Rao (1935, 1954) and Ramachandra Rao (1935) have not been much impressed by the obliteration of the branches of the hepatic veins. Nodules of regeneration have been found to be absent or not very marked. The biliary tree was reported to be normal by Radhakrishna Rao (1935, 1954), but bile duct proliferation in varying degrees was remarked by several authors. Several of the Indian authors have felt that the histological picture of I.C.C. was that of toxic cirrhosis.

Achar and Chacko (1954) examined material from 10 necropsies and 75 liver biopsies from cases which 'clinically looked like infantile biliary cirrhosis'. They paid special attention to the hepatic venous tree and could not demonstrate any obliteration. Srivastava and Aikat (1954) studied the histology of liver biopsy specimens in 45 cases and, on the whole, confirmed the findings of earlier writers; they do not comment on the hepatic veins.

The Liver Diseases Sub-Committee (I.C.M.R., 1955) reported on a careful study of a total of 60 cases in various stages of the disease. They concluded that the basic alteration in the liver in I.C.C. is diffuse liver cell damage and replacement fibrosis. This fibrosis was portal in origin, but might go on to form bands which would then divide the liver into pseudo-lobules, while these pseudo-lobules would in their turn be invaded by fibrous tissue. In other cases, the fibrosis remained diffuse without any attempt at pseudo-lobulation. Occlusion of the hepatic veins was not a feature.

Fernando (1954) describes eight cases with the clinical picture of I.C.C. from Ceylon. The histological appearances were those of intralobular cholangiolitic biliary cirrhosis. Karunaratne (1951) had earlier reported three cases observed in Ceylon and concluded that fibrosis did not originate in the portal tracts.

From Egypt, Hashem (1939) reported a special form of cirrhosis of the liver in children. Pathological findings in three cases were described: acute haemorrhagic necrosis associated with phlebitis and thrombosis of the smaller divisions of the hepatic veins was noted and was a prominent feature in the acute and subacute cases. This was followed by fibrosis and cirrhosis.

From West Africa, Walters and Waterlow (1954) have described fibrosis of the liver observed in Gambian children, of which the aetiology was unknown. The authors suggested the possibility of a dual lesion and a dual aetiology, *viz.*, (*a*) a nutritional or metabolic lesion of the parenchyma, and (*b*) the development of hyper-reactive mesenchymal elements as a result of malaria. A severely fatty liver characteristic of kwashiorkor was never seen, neither was there frank necrosis of parenchymal cells.

In South Africa, Higginson (1956) has recently reported that he has observed four cases of veno-occlusive disease. Suckling and Campbell (1957) have reported from South Africa that the development of a cirrhosis could not be established in a five-year follow-up study of previously treated

kwashiorkor patients. The general tendency at present is to consider that malnutrition and kwashiorkor *per se* are not in themselves responsible for a subsequent fibrosis or cirrhosis of the liver—a view also expressed on the basis of observations in Jamaican infants and children (Bras, 1955).

In Indonesia, Lie and Tjokronegoro (1954) found fibrosis and cirrhosis of the liver relatively frequently in children in Java with or without malignant malnutrition. The malnutrition was apparently not a factor in the production of the fibrosis. They concluded that viral hepatitis or a disease clinically consistent with virus hepatitis might be one of the causes of cirrhosis in this country. One of the present authors (G.B.) has been in the position to study some of their material and shares the opinion expressed by these authors that the histological picture also is not like that of veno-occlusive disease.

Blankhart (1953) reported the relatively frequent occurrence of cirrhosis of the liver in the island of Sangir, lying to the north of Celebes. This condition was clinically diagnosed

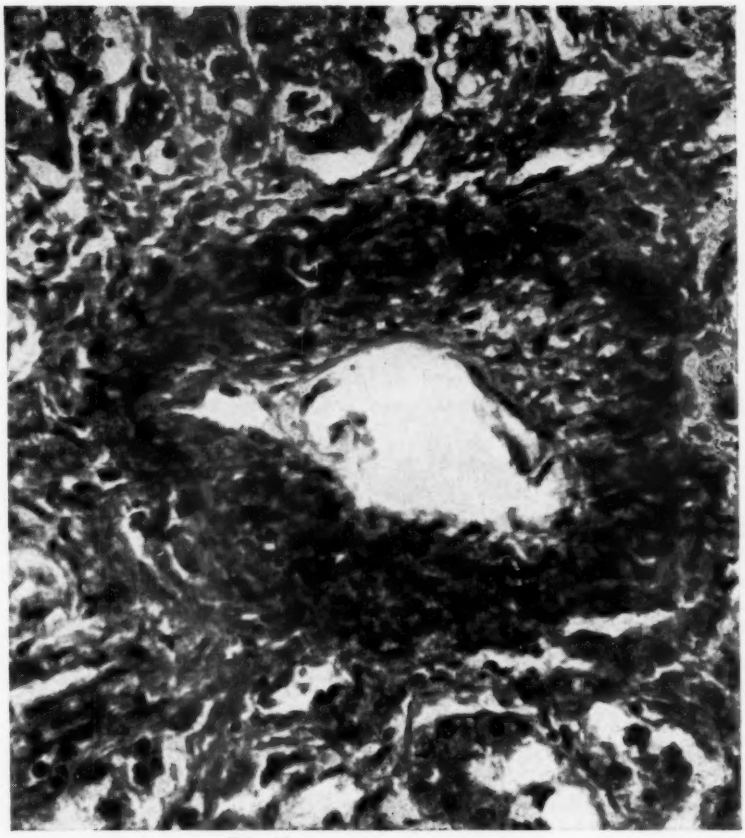

FIG. 13.

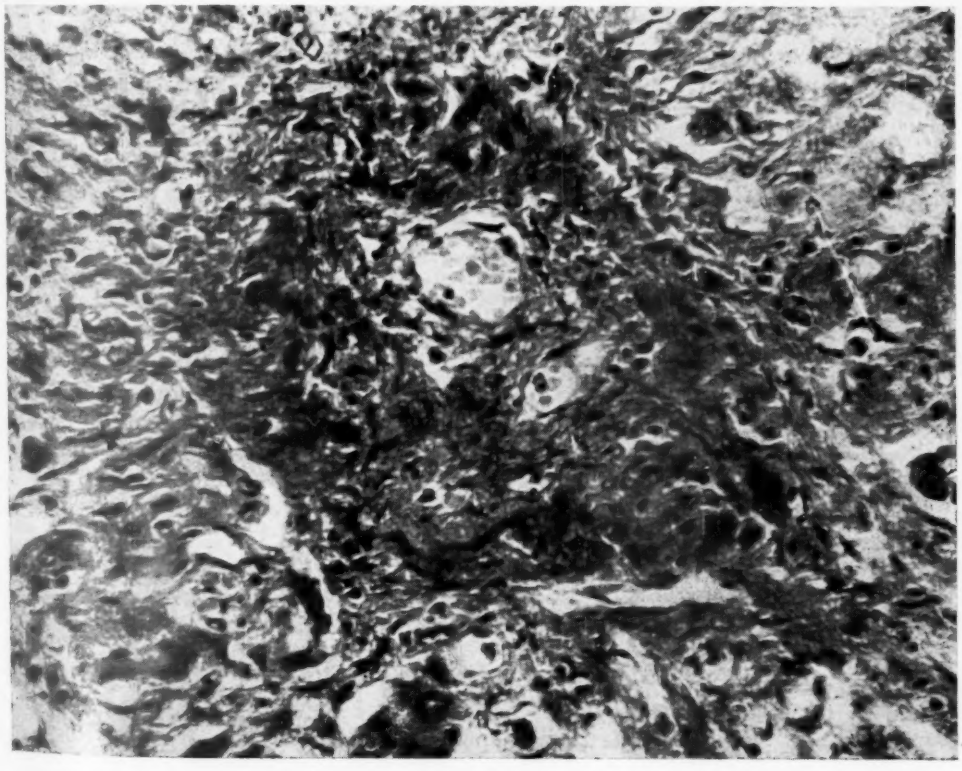

FIG. 14.

FIG. 13.—Marked subendothelial collagenous thickening of hepatic vein branch. Mallory trichome × 340. (Slide of Dr. Y. Bhende of Madras.)

FIG. 14.—Branch of the hepatic vein markedly narrowed; two blood channels lined by endothelium are visible (? recanalization) × 340. (Slide of Dr. Y. Bhende of Madras.)

in 32 children under 15 years of age, but was not seen in those younger than 5 years. Histology was difficult to obtain, but whilst working in Indonesia one of the present writers (G.B.) was able to examine some of Blankhart's material. The cirrhosis seen was histologically well advanced and, although occasionally veno-occlusion of branches of the hepatic vein was observed, it could not be excluded that this was a sequel to the cirrhosis rather than a primary lesion.

From Europe, a condition of obliteration of hepatic veins, named endophlebitis hepatica obliterans, occurring in infants and children, has been reported. Wurm (1939) reported eight cases at the age of 3 months, all ending fatally. A bacterial toxic aetiology through artificial feeding was incriminated. Burkhardt (1938) saw this condition in a 2-year-old child for which he postulated an allergic cause. Konig (1943) observed the condition in a newborn child and postulated intoxication by the transplacental route.

A number of other conditions leading to occlusion of the hepatic veins have been reviewed in a previous publication (Bras *et al.*, 1954). Various conditions of the liver giving rise to fibrosis and/or cirrhosis in children have been described, such as syphilis and the more obscure types exhaustively reviewed by Rössle (1930). More recently erythroblastosis (Craig, 1950) and fibrosis in children with acute leukaemia following folic acid antagonists (Colsky, Greenspan and Warren, 1955) have been reported. These do not at present warrant further discussion with regard to the cases reported here.

DISCUSSION

A condition in the liver, with obliteration of hepatic veins as a predominant feature, has been established beyond doubt as occurring in infants and children. The reports from Jamaica, Egypt, India, South Africa and Europe, submitted by different authors, substantiate this. In Jamaica, Egypt, South Africa, Europe and some cases from India—such as those of Rhadakrishna Rao and Ramchandra Rao, some of Bhende's and Deoras' cases, as well as the Indian children reported in the present paper—this obliteration is prominent and has been of sufficient importance to be considered by the various investigators to be responsible for the development of fibrosis and cirrhosis subsequent to the obstruction, or, at least, to have played an important role in the development of fibrosis and cirrhosis. On the other hand, there are several writers from India who have expressly denied the presence of hepatic venous lesions and it is obvious that more study is needed to clarify this point. Unlike the picture in Jamaica, I.C.C. does not appear to have the characteristic acute episode with the development of massive ascites, which separates this entity quite clearly from any other. Much of the study in I.C.C. has therefore necessarily been performed on well-established cases of cirrhosis and every histopathologist knows that in such an event a recapitulation of the morphogenesis is frequently impossible. On the basis of studies in cirrhotics in Jamaica, it is suspected that at least some of the vessels called by Indian workers patent hepatic vein branches are in fact examples of collateral circulation. Injection studies of the hepatic veins with radio-opaque material (Stuart and Bras, 1957) may assist considerably here. In addition, it is by no means certain that all the authors describing I.C.C. have indeed reported on one disease entity only, instead of on a variety of diseases which have liver damage and subsequently fibrosis in common.

It seems, however, improbable that the liver cell degeneration and necrosis so uniformly observed by all the students could in all cases be secondary to veno-occlusion. This mechanism was accepted in Jamaica for veno-occlusive disease since all cases had sufficient changes in the hepatic veins to explain the centrilobular necrosis observed, even though the Jamaican workers have always stressed the fact that hepato-cellular damage, either primary or concurrent, but independent, of the hepatic venous occlusion, cannot be excluded. It appears necessary that post-mortem vascular injection studies of the liver should be done in I.C.C.

Analogous controversial statements exist in the veterinary literature. Experimental work on poisoning with certain toxic plants (*Crotalaria sp.* and *Senecio sp.*) has demonstrated liver cell damage which has been extensively commented upon by some authors (Bras *et al.*, 1957). Other authors working with the same plant species noticed changes of the hepatic veins; whilst, in South Africa, *Senecio* poisoning in man has been observed to produce hepato-venous occlusion (Selzer and Parker, 1951). Our own experiments on rats with *Senecio* and *Crotalaria* have produced extensive liver cell degeneration and necrosis in many animals without changes in the hepato-venous tree, while in some other animals a disease indistinguishable from human veno-occlusive disease has been produced. Lastly, *Crotalaria* fed to cattle in Jamaica has also resulted in veno-occlusive disease and fibrosis.

It would, therefore, appear acceptable to postulate that toxic liver damage in children may produce either liver cell degeneration and necrosis concurrent with changes in the cholangioles as described in cholangiolitic cirrhosis (Rössle, 1930; Watson and Hoffbauer, 1946), or hepato-venous changes,

or both. This certainly appears to be the case in such experimental animals as rats, cattle, horses. Experiments are at present being conducted with the object in view of trying to separate the parenchymal toxic component from the vascular toxic component.

SUMMARY

Cirrhosis of the liver is common in children in parts of India, especially in West Bengal and Madras, and in the West Indian island of Jamaica, where it usually occurs as a late result of 'veno-occlusive disease of the liver'. The literature concerning veno-occlusive disease is reviewed, with especial reference to its possible relation to the ingestion of plant toxins of certain 'bush teas', particularly species of *Crotalaria* and *Senecio*.

The clinical and pathological features of 15 cases of Indian childhood cirrhosis (I.C.C.) seen in Calcutta, West Bengal, are presented, analysed and compared with accounts in the literature. A two-stage clinical classification is suggested: (1) stage of hepatomegaly, (2) stage of clinical cirrhosis. The socio-economic background of the present cases is compared with reports by previous workers.

The clinical picture and morbid anatomy of veno-occlusive disease and I.C.C., as judged by the literature and the present cases, are compared and contrasted. While some cases are clinically similar, the absence in I.C.C. of the acute episode that occurs in some children with veno-occlusive disease is stressed. Hepatic venous occlusion was found in all six of the 15 children who were liver biopsied or who came to necropsy. This histological feature has been noted by some other investigators, although more workers have stressed the presence of parenchymal damage.

It is noted that, in both experimental animals and in veterinary medicine, it has been shown that certain plant toxins may sometimes act on liver cells and sometimes on the hepatic veins. The possibility of a similarly varied response in children is suggested.

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REFERENCES

Achar, S. T. and Chacko, R. (1954). *Indian J. med. Sci.*, **8**, 442
Asprey, G. F. and Thornton, P. (1953). *W. Indian med. J.*, **2**, 233.
Beaver, P. C., Snyder, C. H., Carrera, G. M., Dent, J. H. and Lafferty, J. W. (1952). *Pediatrics*, **9**, 7.
Bhende, Y. M. and Deoras, S. M. (1954). *Indian J. med. Sci.*, **8**, 21.
Blankhart, D. M. (1953). *Docum. Med. geogr. trop. (Amst.)*, **5**, 7.
Brahmachari, U. and Brahmachari, P. (1938). In *The British Encyclopaedia of Medical Practice*, Vol. 8, p. 132. London. Quoted by Indian Council of Medical Research Report (1955).
Bras, G. R. (1955). In *Protein Malnutrition*. Proceedings of a Conference in Jamaica (1953), ed. Waterlow, J. C. Cambridge.
—— and Berry, D. M. (1956). *W. Indian med. J.*, **5**, 37.
——, —— and György, P. (1957). In press.
—— and Hill, K. R. (1956). *Lancet*, **2**, 161.
——, Jelliffe, D. B. and Stuart, K. L. (1954). *A.M.A. Arch. Path.*, **57**, 285.
—— and Watler, D. C. (1955). *W. Indian med. J.*, **4**, 201.
Burkhardt, L. (1938). *Frankfurt Z. Path.*, **52**, 567.
Chatterjee, D. (1940). *Indian med. J.*, **34**, 266.
Chaudhuri, K. C. (1944). *Indian J. Pediat.*, **11**, 61.
Colsky, J., Greenspan, E. M. and Warren, T. N. (1955). *A.M.A. Arch. Path.*, **59**, 198.
Craig, J. M. (1950). *Ibid.*, **49**, 665.
Davidson, J. (1935). *J. Path. Bact.*, **40**, 285.
Fernando, P. B. (1954). *J. Child. Hosp. Colombo*, **3**, 3.
Gibbons, J. B. (1888). *Indian med. Gaz.*, **23**, 52.
Hashem, M. (1939). *J. roy. Egypt. med. Ass.*, **22**, 319.
—— (1948). *Ibid.*, **31**, 541.
Hill, K. R., Rhodes, K., Stafford, J. L. and Aub, R. (1953). *Brit. med. J.*, **1**, 117.
Higginson, J. (1956). Proc. Kampala Conf. on Cancer of the Liver.
Indian Council of Medical Research (1955). *Indian J. med. Res.*, **43**, 723.
Jelliffe, D. B., Bras, G. and Stuart, K. L. (1954a). *Ann. trop. Med. Parasit.*, **48**, 386.
——, ——, —— (1954b). *Pediatrics*, **14**, 334.
Karunaratne, W. A. E. (1951). In *Liver Disease: Ciba Foundation Symposium*, p. 106. London.
König, J. (1943). *Virchows Arch. path. Anat.*, **311**, 527.
Krishna Rao, P. (1950). *Indian med. Gaz.*, **85**, 150.
Lahiri, S. C. (1936). *Ibid.*, **71**, 313.
Lie, K. J. and Tjokronegoro, S. (1954). *Docum. Med. geogr. trop. (Amst.)*, **6**, 193.
McFarlane, A. L. and Branday, W. J. (1945). *Brit. med. J.*, **1**, 838.
Prabhu, M. B. (1940). *Indian J. Pediat.*, **7**, 121.
Radhakrishna Rao, M. V. (1934). *Indian J. Pediat.*, **1**, 166.
—— (1935). *Indian J. med. Res.*, **23**, 69.
—— (1954). *Malnutrition in African Mothers, Infants and Young Children*. Report of 2nd Inter-African Conference on Nutrition, Gambia, 1952, pp. 101, 147, 358. London.
Ramachandra Rao, P. 1935). *Cirrhosis of the Liver*. Ph.D. Thesis. London. Cited by Brahmachari, U. and Brahmachari, P. (1938).
Rhodes, K. (1952). *Brit. J. Nutr.*, **6**, 198.
Rössle, R. (1930). In *Handbuch der speziellen pathologischen. Anatomie und Histologie*, ed. Henke, F. and Lubarsch, O., band 5, teil 1, p. 449. Berlin.
Selzer, G. and Parker, R. G. F. (1951). *Amer. J. Path.*, **27**, 885.
Sen, B. C. (1887). *Indian med. Gaz.*, **22**, 338.
Sherlock, S., Summerskill, W. H. J., White, L. P. and Phear, E. A. (1954). *Lancet*, **2**, 453.
Srivastava, J. B. and Aikat, B. K. (1954). Trans. Sympos. on Liver Injury, Gwalior, Ind. Ass. Path., Bombay, p. 30. and in *Indian J. med. Sci.*, **8**, 446.
Stein, H. (1957). *Brit. med. J.*, **1**, 1946.
Stuart, K. L. and Bras, G. (1955). *Brit. med. J.*, **2**, 348.
——, —— (1956). *W. Indian med. J.*, **5**, 33.
——, —— (1957). *Quart. J. Med.*
Suckling, P. V. and Campbell, J. A. H. (1957). *J. trop. Pediat.*, **2**, 173.
Walters, J. H. and Waterlow, J. C. (1954). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 285.
Waterlow, J. C. (1948). *Ibid.*, No. 263.
Watson, C. J. and Hoffbauer, F. W. (1946). *Ann. intern. Med.*, **25**, 195.
Wurm, H. (1939). *Klin. Wschr.*, **18**, 1527.

Addendum

A recent paper from South Africa has reported three typical cases of veno-occlusive disease in African children under the age of 18 months. All were verified at necropsy (Stein, 1957).

DECIDUOUS TOOTH ERUPTION

BY

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(RECEIVED FOR PUBLICATION MAY 15, 1957)

There is little information concerning deciduous tooth eruption pertaining to children of the United Kingdom and Europe. Therefore, data on children from the current longitudinal growth study at the Child Study Centre, London, were examined. For details of this sample, method of recruitment, and investigations carried out, etc., reference may be made to Moore, Hindley and Falkner (1954). Briefly, this unselected sample of approximately 200 children consists of the same 'healthy' children regularly and periodically seen and drawn from an area in London.

The children are seen at the ages of 4 weeks (± 2 days), 13, 26, 39 weeks, 1 year, 18 months (± 7 days), 2 years and thereafter yearly (± 14 days). The state of dentition is noted at each visit and for the purpose of this paper the total number of erupted teeth is given. The definition of eruption used is that stage when part of the crown of the tooth has pierced the gum (Robinow, Richards and Anderson, 1942; Doering and Allen, 1942; Falkner, 1955, 1957a).

Distribution

Table 1 gives the mean numbers of erupted deciduous teeth present at each age (correct to one decimal place). Boys and girls are separated.

There is a great variation in the number of teeth being erupted between each age level after eruption has begun, and the distribution curves showing total number of erupted teeth are skewed to the right, especially during the period of maximum eruption activity, *i.e.*, 39 weeks to 18 months (Doering and Allen, 1942). Hence, standard deviations are not presented as data, and for the range of 'likely normality', percentiles are given for boys and girls combined.

Table 2 shows the increments of the number of teeth erupting between the various ages.

Only those children seen at the beginning and end of each age period may be included in these calculations, for not every child is able to be present for every planned examination. It was obviously convenient to use the unit of 13 weeks (approximately three months) as the constant incremental period so as to compare rates of eruptions. Some of the periods are not 13 weeks. The period, for example, between the examinations at 4 weeks and 13 weeks is only nine weeks, and this figure has been adjusted to bring it to a 13 weeks' increment (adjusted increment). This is not entirely permissible for it presumes a straight line rate of eruption which may not be the case. However, since the incremental periods are close together in time the adjustments are felt to be justified for this purpose.

The incremental distribution curve of erupted

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TABLE 1

MEAN NUMBER OF ERUPTED TEETH AT GIVEN AGES IN BOYS AND GIRLS

Subject	4 Weeks	13 Weeks	26 Weeks	39 Weeks	1 Year	18 Months	2 Years	3 Years
Boys:								
No.	96	93	90	85	82	79	59	35
Mean	0	0	0·4	2·5	6·2	12·6	16·3	19·9
Girls:								
No.	96	91	84	76	77	68	57	30
Mean	0	0	0·4	3·1	6·1	13·0	16·3	20·1
Boys and Girls:								
No.	192	184	174	161	159	147	116	65
Mean	0	0	0·4	2·8	6·1	12·9	16·3	20·0
5th p.	—	—	0	0·2	2·3	7·0	12·9	20·0
95th p.	—	—	2·8	7·7	9·7	16·0	20·6	21·0

TABLE 2
MEAN INCREMENTS OF TEETH ERUPTED IN 13-WEEK PERIODS

	4–13 Weeks†	13–26 Weeks	26–39 Weeks	39 Weeks–One Year	1 year–18 Months†	18 Months–2 Years†	2–3 Years†
Boys:							
No.	92	86	79	74	65	56	31
Mean increment	0	0·3	2·0	3·7	3·0	1·9	1·0
S.D.*	—	0·8	1·7	2·1	1·2	1·3	0·5
Girls:							
No.	91	83	70	68	58	49	29
Mean increment	0	0·3	2·7	2·9	3·4	1·5	1·0
S.D.	—	0·7	2·0	1·7	1·2	1·0	0·9
Boys and Girls:							
No.	183	169	149	142	123	105	60
Mean increment	0	0·3	2·4	3·3	3·2	1·7	1·0
S.D.	—	0·8	1·9	2·0	1·1	1·2	0·7

* Standard deviation † Adjusted increments

teeth is much more regular and although skewed to the left, the figures are probably fairly normally distributed.

Fig. 1 shows graphically the data from Tables 1 and 2. The fifth and 95th percentiles are given. Children falling outside this band may be suspected of being abnormal in this respect. The percentiles here are those of the total group, boys and girls, for the two sexes so clearly approximate each other as can be readily seen.

Pattern of Eruption

There is a wide range of variation in the number of erupted teeth present at the various ages. The most active period of tooth eruption is between 9 and 18 months.

Table 3 shows the numbers of children erupting their first deciduous tooth in the periods listed.

These children had no teeth present at the beginning of the incremental period, but had developed one or more when seen at the end of the incremental period.

No child examined had any teeth at 4 or 13 weeks, while three boys erupted their first tooth between 1 year and 18 months. No girl was as late as this and no children had failed to erupt at least one tooth by 18 months.

Regarding the completion of deciduous dentition, Table 4 shows the percentages of the children examined at these ages who had completed deciduous dentition.

TABLE 4
PERCENTAGE OF CHILDREN COMPLETING DECIDUOUS DENTITION

Age (yr.)	Boys (%)	Girls (%)
2	11·8	10·5
3	100·0	100·0

Sex Differences

Robinow *et al.* (1942) found that boys were less variable in the pattern of deciduous tooth eruption and were in advance of the girls in all teeth except the first molar. Meredith (1946) demonstrated a tendency for the process in boys to be two weeks in advance of girls, and Doering and Allen (1942) that, althought not statistically significant, on the average males consistently have more deciduous teeth at every age except 3 years. MacKay and Martin (1952), studying small groups of African children at three-monthly intervals, also found the male consistently, if slightly, in advance of the female.

Comparing means of total teeth erupted of the London children does not show that there is any significant difference between the sexes, and the small spaced time intervals of the examination on the same children do not show any consistent advance of means of one sex over the other. Similarly, no significant difference in the sexes were

TABLE 3
NUMBERS OF CHILDREN ERUPTING THEIR FIRST DECIDUOUS TOOTH

Subject	0–4 and 4–13 Weeks	13–26 Weeks	26–39 Weeks	39 Weeks–1 Year	1 Year–18 Months
Boys	0	16 (18·6%)	48 (60·7%)	20 (27·0%)	3 (4·6%)
Girls	0	17 (20·5%)	46 (65·7%)	14 (20·6%)	0 (0%)

Note—The percentages given are of the number of children actually seen at the end of each incremental period (Each child may not be present for each appointed examination. Hence, the percentages will not total 100%.)

found in a recent comparative study including four European samples and one African sample of children (Falkner, Habich, Pernot and Sénécal, 1957). Comparison of early and late eruptors in both sexes showed no trend or significant difference between the sexes.

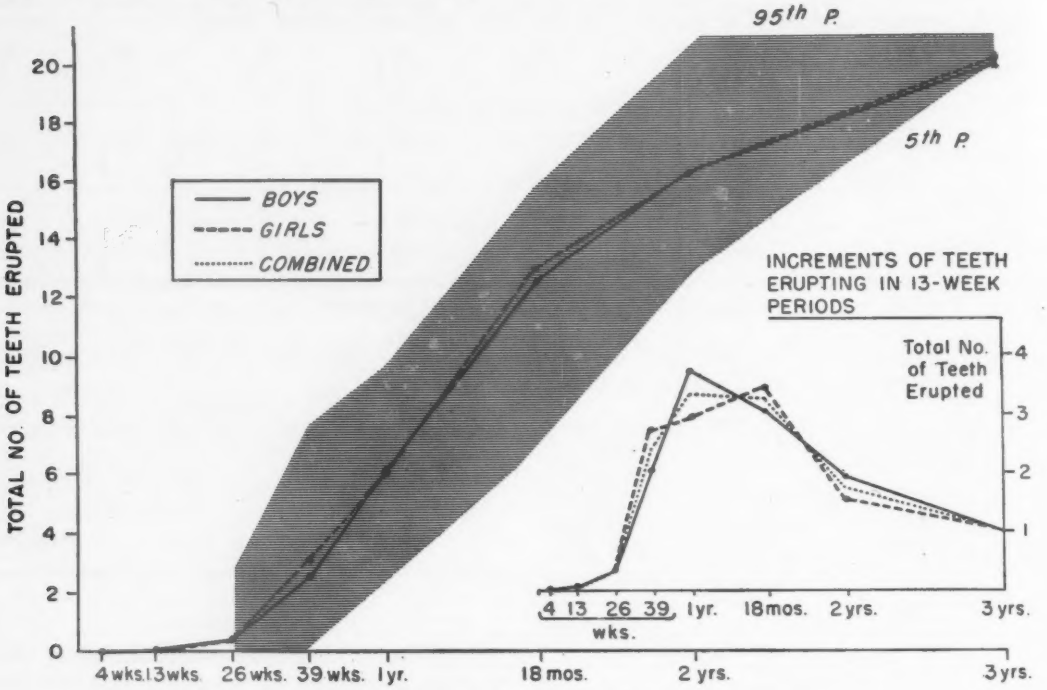
95th P.
5th P.
BOYS
GIRLS
COMBINED
TOTAL NO. OF TEETH ERUPTED
INCREMENTS OF TEETH ERUPTING IN 13-WEEK PERIODS
Total No. of Teeth Erupted
4 13 26 39 1yr. 18mos. 2yrs. 3yrs.
wks.
4 wks. 13 wks. 26 wks. 39 wks. 1 yr. 18 mos. 2 yrs. 3 yrs.

FIG. 1.—The distance and velocity curves of deciduous tooth eruption.

Deciduous and Permanent Dentition

Parfitt (1954) has described the age of shedding of deciduous and permanent teeth, and, as he points out, the age of eruption of the permanent teeth may be affected by early shedding of deciduous teeth. Although rare, deciduous teeth are shed in the age range described here. One tooth was shed from each child, and in two children, one tooth each was extracted after injury. These children have been excluded from this series. In this group one child had one permanent tooth at 3 years, while one had two at 3 years.

It is clear that permanent dentition investigated in a wide variety of races is a maturational indicator (Hurme, 1949; Boas, 1933; Clements, Davies-Thomas and Pickett, 1953; Cattell, 1928a and b; Steggerda and Hill, 1942; Suk, 1919; Palmer, Klein and Kramer, 1938), and related to some extent to other morphological processes, including sexual maturity (Tanner, 1955), and that here girls are in advance of boys. There is a particular spurt of eruption in girls around 9 years of age (Suk, 1919), presumably related to the near-puberty state. These children will be followed to test this hypothesis, and it will be interesting to see if deciduous

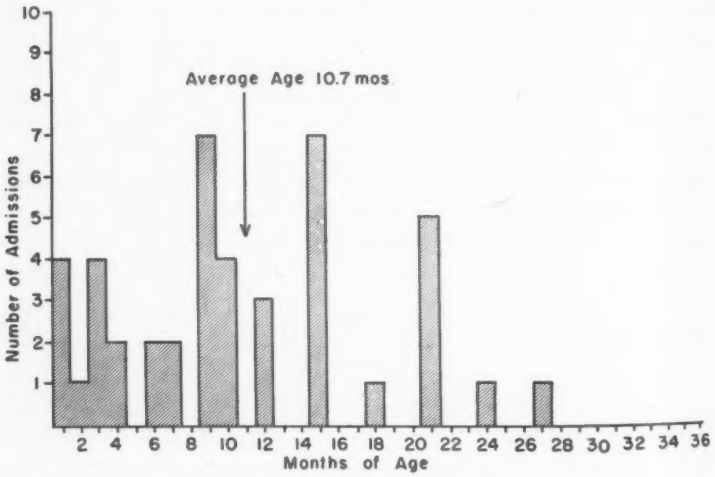

FIG. 2.—Histogram showing ages at which the children were admitted to hospital (see page 391).

TABLE 5
MEAN LYING-LENGTH OF ADVANCED ERUPTORS (BOYS AND GIRLS COMBINED) AND TOTAL GROUP (BOYS AND GIRLS COMBINED) IN CM. (TO THE NEAREST 0·1 CM.) AT INDICATED AGES

	4 Weeks	13 Weeks	26 Weeks	39 Weeks	1 Year	18 Months	2 Years	3 Years
Advanced eruptors ..	(9) 51·7	(9) 58·4	(9) 65·0	(9) 68·6	(8) 73·0	(7) 78·7	(9) 82·7	(7) 90·7
Rest of total group ..	53·3 (150)	59·3 (172)	65·8 (166)	70·5 (153)	74·2 (150)	80·6 (136)	85·7 (100)	94·7 (142)
P	<·02>·01	<·2>·1	<·6>·5	<·05>·02	<·3>·2	<·001	<·02>·01	<·05>·02

* Figures in brackets indicate number examined at each age. 'P' figures shown for each age, were computed by the 't' test.

dentition is in fact 'separate' from permanent dentition in this respect; for if this hypothesis is correct the advance of one sex over the other is reversed, or makes its appearance (if in fact there is no difference in sexes in the deciduous period) at the completion of deciduous dentition. It has not been shown to date whether the two processes of dentition are related in any way. Kihlberg and Koski (1954) argue that if both deciduous and permanent eruption curves are stabilized by the use of logarithms and post-conceptional age, then both processes follow the same biological laws and there is little difference in the sexes.

Maturation

Tanner (1955), reviewing data (Spier, 1918; Wallis, 1931; Shuttleworth, 1937, 1939), has shown that permanent dentition is clearly to some extent positively related to morphological advancement as indicated by skeletal maturity and height but it is not a strong relationship.

Hellman (1923, 1930) in fact states that tall children erupt their permanent teeth later. Table 5 shows comparative figures between the two groups of children in this study, the 'advanced tooth eruptors' and the rest of the sample excluding these children.

The 'advanced eruptors' were selected by virtue of being the only children who had all their deciduous teeth by 2 years. There were 10 'advanced' children, six girls and four boys. Two had all their deciduous teeth by 18 months and eight had all by 2 years.

These 'advanced' children are consistently smaller, as indicated by their lying-length, at each age. By inspection of the data at each age it can be seen that they are highly significantly so at 18 months; at 4 weeks and 2 years, and less so at 3 years and 39 weeks. Clearly smaller babies (by lying-length estimation in this sample) erupt their deciduous teeth at a more rapid rate. It is known that on average by studies on the older child (Bayley, 1943, 1956; Acheson and Hewitt, 1954, etc.) children shorter than the average at particular ages reach their puberty later. It is interesting, therefore, that these children are advanced in deciduous tooth eruption which might have been supposed to be a maturational factor. With this in mind the skeletal maturity of the 'advanced eruptors' was assessed by the method of Acheson (1954) which allows of an adequate measure of this factor (Falkner, 1957b). Since girls are well in advance of boys in this pattern of development it was necessary to separate the sexes, and, although in nearly every case the advanced eruptors were delayed in skeletal maturation compared to the rest of the sample, no definite conclusions could be drawn.

Since Acheson and Hewitt (1954) have shown that retardation in skeletal status is correlated in some measure to a like retardation in height, a very necessary step was to determine if there were any correlation between skeletal maturity and deciduous dentition as a whole. Correlation coefficients of from +0·03 to +0·07 were found at all ages and with the sexes separated showing no relationship between

TABLE 6
MEAN NUMBER OF TOTAL ERUPTED TEETH AT GIVEN AGES (BOYS AND GIRLS COMBINED)

Age	U.S.A. (Doering and Allen, 1942)	U.S.A. (Meredith, 1951 a & b)	London (1957)	Paris (1957)	Zurich (1957)	Dakar (1957)
6 months	0·4	—	0·4	0·4	0·4	—
9 months	3·1	3	2·8	2·9	2·5	2·7
1 year	5·9	6	6·1	5·8	5·4	4·7
1 year 6 months ..	12·4	13	12·9	12·3	12·2	11·4
2 years	16·7	17	16·3	16·4	16·3	16·4
3 years	19·9	20	20·0	—	—	—

these two processes. Perhaps this is not so surprising since bone is derived from mesoderm, and the teeth, in part, are epithelial.

Race

Table 6 shows the comparative means of total teeth erupted from six sources (Doering and Allen, 1942; Meredith, 1951a & b; Falkner *et al.*, 1957).

It is not very surprising how similar the means are for American and European children, but perhaps it is so in the case of African children from Dakar. Steggerda and Hill (1942) found there were racial differences in the permanent tooth eruption patterns and that in a study of four races, Navajo, Negro, Maya and White were advanced over the other in that order. Garn and Moorrees (1951) showed that permanent tooth eruption was markedly advanced in Aleutian Aleuts over white children. Evidence is accumulating that the African child is in advance of the European in many phases of development in early life (Dean, 1956; Falkner *et al.*, 1957, etc.), and Allbrook (1956) has shown that there is a reduction in the adrenal cortical mass in the East African compared to the European, and such work stimulates speculation on the basis for these differing patterns. Again, potential malnutrition might have been expected to delay the African child's deciduous dentition. Since practically all these African children have access to excess quantities of breast milk, it is unlikely that malnutrition will develop early enough to affect deciduous dentition nor incidentally other developmental factors (Sénécal, 1956; Falkner *et al.*, 1957). On the other hand poor maternal prenatal nutrition might have been thought to affect this pattern.

Data on siblings (Robinow *et al.*, 1942) and twins (Tisserand-Perrier, 1953) show that the deciduous eruption pattern is largely influenced by hereditary factors. The genetic element in racial characteristics is of course very large. Further work is needed on this subject.

Here the similarity of means bears out the growing evidence accumulated in this paper and previously (Robinow *et al.*, 1942) that deciduous dentition appears nonchalantly independent of most usually correlated developmental processes.

Illness

In trying to assess the effect of illness on morphological processes there is the great difficulty in defining what is an illness, and further to rate its severity. In estimating whether the traditional belief that illness retards deciduous dentition was true or false, an alternative method was followed which obviates some of the difficulties mentioned.

In the total sample, 37 children were in hospital in the period of their first three years of life, and none of the others were. Seven were in hospital twice, but no child more than this. There were, therefore, 44 hospital admissions. All the admissions were to a teaching children's hospital, to one of the two isolation hospitals, or to a special unit of a teaching hospital for a specific treatment. Beds for admission of children under 3 years are limited at the children's hospital mentioned by two factors: pressure on beds available; and a very laudable unwillingness of the responsible admitting physicians to take in any child unless really necessary. This applies also to the isolation hospitals. Therefore, it is claimed, fairly one would think, that any child being in hospital in this period was ill to a reasonably and comparatively severe degree. Having been admitted they then were under the influences of their disease and hospital life *per se*.

Table 7 shows the state of deciduous eruption of the two groups: children who had been in hospital; and the rest of the sample who had not.

The children who had been in hospital up to and including 1 year of age had always fewer teeth than those not admitted. This difference was significant at 26, 39 weeks and 1 year of age with boys and girls

TABLE 7

MEANS OF TOTAL ERUPTED TEETH IN CHILDREN ADMITTED AND NOT ADMITTED TO HOSPITAL (BOYS AND GIRLS, AND SEXES COMBINED)

	Admitted to Hospital	Not Admitted	P
Boys: 26 weeks	0·2 (19)	0·5 (71)	·05
Girls: 26 weeks	0·3 (13)	0·4 (71)	>·7
Boys and Girls: 26 weeks	0·2 (32)	0·5 (142)	<·1>·05
Boys: 39 weeks	1·7 (16)	2·6 (69)	<·2>·1
Girls: 39 weeks	2·5 (13)	3·2 (63)	<·3>·2
Boys and Girls: 39 weeks ..	2·1 (29)	2·9 (132)	<·2>·05
Boys: 1 year	5·5 (18)	6·2 (64)	<·4>·3
Girls: 1 year	4·4 (12)	6·2 (65)	<·2>·1
Boys and Girls: 1 year	5·4 (30)	6·2 (129)	< ·01

* Figures in brackets are numbers of children involved. 't' Test computed and 'P' figures given up to one year.

combined and for the boys alone at 26 weeks. There was no trend and no significant difference after 1 year of age. Fig. 2 shows a histogram of the hospital admissions and demonstrates their timing. The average age at time of admission was 10·7 months and indicates a possible cause and effect value between admission to hospital and retardation of deciduous eruption.

Traditional teaching in the lecture hall and some investigators (Robinow, 1942) have sometimes indicated that acute illness softens the gums and hence increases the rate of deciduous teeth eruption. This would appear to be false.

Summary

Means of total erupted deciduous teeth present are given at ages of 4, 13, 26, 39 weeks, 1 year, 18 months, 2 and 3 years in a sample of children longitudinally followed. The fifth and 95th percentiles are given.

The means and standard deviations of increments of erupting teeth are given between the ages stated above.

The distribution curves of total teeth present are discussed and shown to be abnormally distributed. Those of incremental data are nearly normally so.

The general pattern of eruption is discussed in the sexes both from the point of view of the value of deciduous eruption as a maturational indicator and of its relationship to skeletal maturation. It appears that deciduous dentition is remarkably independent of other morphological processes.

In this sample children advanced in deciduous tooth eruption are consistently and significantly smaller than the average during eruption. No relationship is shown between deciduous tooth eruption and skeletal maturation.

Comparisons of deciduous dentition are made between American, European and African children. There is a markedly similar pattern.

It is suggested that the effect of admission to hospital and presumably illness of some severity slows deciduous dentition.

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References

Acheson, R. M. (1954). *J. Anat. (Lond.)*, **88**, 498.
—— and Hewitt, D. (1954). *Brit. J. prev. soc. Med.*, **8**, 59.
Allbrook, D. (1956). *Lancet*, **2**, 606.
Bayley, N. (1943). *Child Developm.*, **14**, 1.
—— (1956). *J. Pediat.*, **48**, 187.
Boas, F. (1927). *J. dent. Res.*, **7**, 245.
—— (1933). *Hum. Biol.*, **5**, 429.
Cattell, P. (1928a). *J. dent. Res.*, **8**, 279.
—— (1928b). *Dentition as a Measure of Maturity*. Cambridge, Mass.
Clements, E. M. B., Davies-Thomas, E. and Pickett, K. G. (1953). *Brit. med. J.*, **1**, 1425.
Dean, R. F. A. (1956). Conference on the Role of Body Measurements in the Evaluation of Human Nutrition, Cambridge, Mass., 1955. (National Research Council.) Reported in *Hum. Biol.*, **28**, 252 (1956).
Doering, C. R. and Allen, M. F. (1942). *Child Developm.*, **13**, 113.
Falkner, F. (1955). Ed. *Une Base-Commune de Récherches pour les Études Longitudinales sur la croissance de l'Enfant*. Centre Int. de l'Enfance, Paris.
—— (1957a). Ed. *Internationally Cooperative Research in Child Development*. (In French and English.) Centre Int. de l'Enfance, Paris. (In the Press.)
—— (1957b). Proceedings Amer. Ass. Phys. Anthrop. *Amer. J. Phys. Anthrop.*, **14**, No 2. (In the Press.)
——, Habich, H., Pernot, M. and Sénécal, J. (1957). *International Comparisons of Growth in First Two Years of Life*. Courrier. CIE, Paris. (In the Press.)
Garn, S. M. and Moorrees, C. F. A. (1951). *Child Developm.*, **22**, 261.
Hellman, M. (1923). *Dent. Cosm.*, **65**, 34 and 1329.
—— (1930). White House Conference on Development of Children, Vol. II, p. 149.
Hurme, V. O. (1949). *J. dent. Child.*, **16**, no. 2, p. 11.
Kihlberg, J. and Koski, K. (1954). *Suom. Hammaslaak. Toim.*, **50**, Suppl. 2, p. 6.
MacKay, D. H. and Martin, W. J. (1952). *J. trop. Med. Hyg.*, **55**, 265.
Meredith, H. V. (1946). *J. dent. Res.*, **25**, 43.
—— (1951a). *Amer. J. Orthodont.*, **37**, 802.
—— (1951b). *J. Pediat.*, **38**, 482.
Moore, T., Hindley, C. B. and Falkner, F. (1954). *Brit. med. J.*, **2**, 1132.
Palmer, C. E., Klein, H. and Kramer, M. (1938). *Growth*, **2**, 149.
Parfitt, G. J. (1954). *Dent. Rec.*, **74**, 279.
Robinow, M., Richards, T. W. and Anderson, M. (1942), *Growth*, **6**, 127.
Sénécal, J. (1956). Personal Communication.
Shuttleworth, F. K. (1937). *Monogr. Soc. Res. Child Dev.*, **2**. No. 5.
—— (1939). *Ibid.*, **4**, No. 3.
Spier, L. (1918). *Dent. Cosm.*, **60**, 899.
Steggerda, M. and Hill, T. J. (1942). *Amer. J. Orthodont.*, **28**, 361.
Suk, V. (1919). *Amer. J. phys. Anthrop.*, **2**, 351.
Tanner, J. M. (1955). *Growth at Adolescence*. Oxford.
Tisserand-Perrier, M. (1953). *J. Génét. hum.*, **2**, 87.
Wallis, R. S. (1931). *Univ. of Iowa Stud. Child Welfare*, **5**, No. 1.

BLOOD OXYGEN STUDIES IN PREMATURE INFANTS

BY

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Certain features peculiar to premature babies appear to justify the routine use of oxygen. Cyanotic attacks are frequent, an irregular respiratory rhythm is common, and in the smaller infants the pulmonary alveoli are incompletely developed and present a thicker barrier than normal between the alveolar air and the blood stream. Graham, Reardon, Wilson, Tsao and Baumann (1950) and Wilson, Long and Howard (1942) have shown that the respirations of a premature baby will become regular when oxygen is administered. Malm (1953) observed an increased uptake of oxygen by small premature babies who were placed in an oxygen-enriched atmosphere and suggested that their previous oxygen consumption was inadequate. The work of Smith and Kaplan (1942), Graham *et al.* (1950) and Taylor (1954) has shown that the blood oxygen saturation in smaller premature infants is lower and subject to wider variations than in full-term infants. It should not, however, be assumed that these features are necessarily harmful to the baby who is born before term, and indeed, they may not require correction.

The work reported in this paper was undertaken in 1954 to determine the oxygen saturation of blood obtained from premature babies by heel stab.

Method

Forty premature babies in the Premature Baby Unit of Walton Hospital, Liverpool, were studied for varying periods from the time of birth to the age of 3 months. Haemoglobin and blood oxygen estimations were made on cutaneous blood obtained by heel stab. It has been shown that the oxygen content of 'cutaneous' blood is almost identical with that of arterial blood provided that there is vasodilatation and a rapid blood flow (Hultgren and Hackett, 1950; Lundsgaard and Möller, 1922). No special effort was made to warm the limb before the sample was taken but all infants were lying quietly in a cot or incubator with a surrounding temperature approaching 90° F. No infant was crying before the heel stab was made but they invariably did so immediately afterwards. After cleansing with ether the heel was stabbed with a sharp Hagedorn needle and the first drop of blood was discarded. The haemoglobin pipette was then filled and the heel wiped dry. Another pipette was then placed over the incision so that there was no contact between the air and the blood that was to be used for oxygen estimation. The oxygen content of this sample was determined immediately.*

The haemoglobin was estimated by the Medical Research Council Grey wedge photometer, the accuracy of the instrument in use being checked at intervals. The oxygen content was estimated by the microgasometric method of Roughton and Scholander (1943). This method has certain advantages over the standard Van Slyke procedure in that it is simple and rapid and requires only a very small quantity of blood. It is accurate to about 0·15 volumes %.

The oxygen capacity of the blood was obtained by calculation from the haemoglobin content, assuming that 1 g. of haemoglobin combines with 1·34 ml. of oxygen (Hüfner, 1894). The amount of oxygen in simple solution was subtracted from the total oxygen content as obtained from the Roughton-Scholander estimation in order to obtain the amount of oxygen combined with the haemoglobin, using the formula:

$$\text{Dissolved oxygen (vol.)} = pO_2 \times O_2$$

(where pO_2 = partial pressure of oxygen in lungs, and O_2 = Bunsen solubility coefficient.)

To determine the effect on the blood oxygen concentration of raising the oxygen content of the inspired air, infants were placed under a 'perspex' hood in an atmosphere of 55 to 60% oxygen for one hour, blood samples being collected before and at the end of this period. The oxygen content of the air-gas mixture was determined by a simple pyrogallol apparatus.

Results

Haemoglobin. Fig. 1 demonstrates the marked fall in haemoglobin during the first eight weeks of life. During the first week of life the mean haemoglobin level was almost 20 g. per 100 ml., by the end of the fourth week it was only 13 g. per 100 ml. and by the eighth week only 9·8 g. per 100 ml.

Oxygen Content. The fall in oxygen content during the first eight weeks of life is indicated in Fig. 2. During the first week of life the mean blood

* All estimations reported in this paper were made by P.M.R.

oxygen content was 23 vol. % with individual readings varying between 14·9 and 30·7 vol. %. By the end of the fourth week the average oxygen content had fallen to 16 vol. % with individual readings varying between 9·2 and 20·0 vol. %. By the eighth week there had been a further fall to 10·0 vol. % with a range from 7·8 to 12·6 vol. %. (The oxygen content of blood with a haemoglobin content of 14·8 g. per 100 ml., which is 100% saturated with oxygen, is 19·8 vol. %.)

Percentage Oxygen Saturation. The fall of blood oxygen content during the first eight weeks of life parallels the fall in haemoglobin which occurs during the same period. The percentage oxygen saturation of the blood, therefore, remains about the same.

Fig. 3 is a scattergram showing all the values obtained for blood oxygen saturation charted according to age. The mean blood oxygen saturation of the 238 determinations on 40 infants was 88·8% (S.D. 8·8) with a range of values from 61·5% to 102·5%.

Table 1 demonstrates the distribution of results obtained for blood oxygen saturation. Though almost half the samples examined were over 90% saturated, a considerable number (16·4%) were less than 80% saturated with oxygen.

TABLE 1
PERCENTAGE OXYGEN SATURATION OF CUTANEOUS BLOOD IN 40 INFANTS

Oxygen Saturation (%)	No. of Readings	Percentage
Below 70	6	2·5
70–79	33	13·9
80–84·9	31	13·0
85–89·9	50	21·0
Over 90	118	49·6

Mean oxygen saturation of blood=88·8% (S.D. 8·8).
Range of values=61·5%–102·5%.

It was found that infants of lower birth weight tended to have lower blood oxygen saturations (Table 2). The average blood oxygen saturation of infants weighing less than 3½ lb. (1·6 kg.) at birth was 86·0% (S.D. 9·5) compared with 90·1% for infants weighing over 4½ lb. (2 kg.) at birth.

TABLE 2
BLOOD OXYGEN SATURATION AND BIRTH WEIGHT

Birth Weight (lb.)	Mean Saturation (%)	S.D.
Under 3½	86·0	9·5
3½–4	89·9	8·5
4–4½	88·5	8·5
Over 4½	90·1	8·5

(*a*) Mean oxygen saturation and birth weight.

Fig. 4 and Table 3 compare the values of blood oxygen saturations of premature and full-time infants. The mean percentage oxygen saturation of premature infants (88·8%) was lower than that of the full-time infants (93·0%), the range of values was greater, and more low figures were recorded. Similar investi-

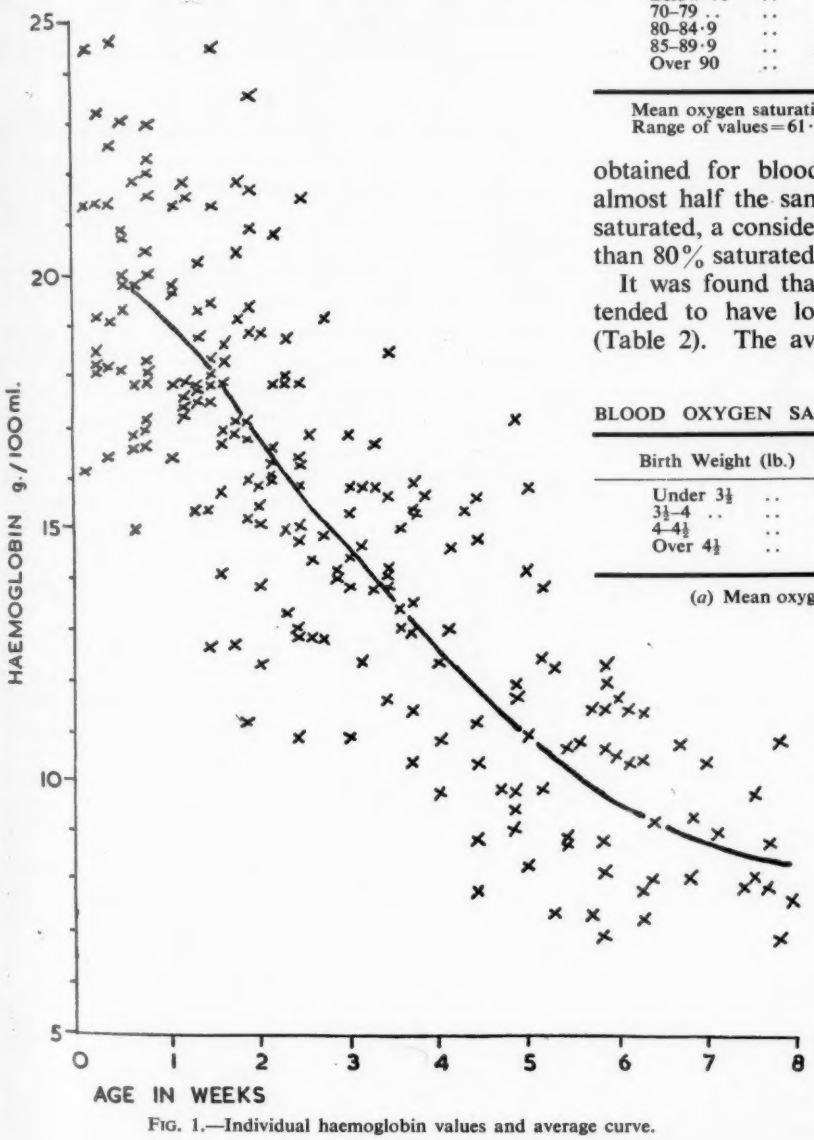

FIG. 1.—Individual haemoglobin values and average curve.

gations on 13 adults gave a mean blood oxygen saturation of 96·4%.

The Results of Administration of Oxygen. The administration of oxygen for short periods to our premature infants resulted in an increase in the oxygen content and saturation of the blood on 21 of the 23 occasions on which it was given. The extent of the increase was not related to the initial oxygen content but was in general related to the initial oxygen saturation of the blood, the lower the initial saturation the greater the increase after giving oxygen. A final blood oxygen saturation of over 97% was reached by more than half the infants, and 19 of the 23 had final saturations over 90%. Details are given in Table 4.

TABLE 3
COMPARISON OF FULL-TERM AND PREMATURE INFANTS

Mean % Saturation: Premature: 88·8% (S.D. 8·8).
Full-term: 93·0% (S.D. 6·47).
The difference between the two groups is significant (t = 3·93).
Range of values: Premature: 61·5 to 102·5%.
Full-term: 78·3 to 104·0%.

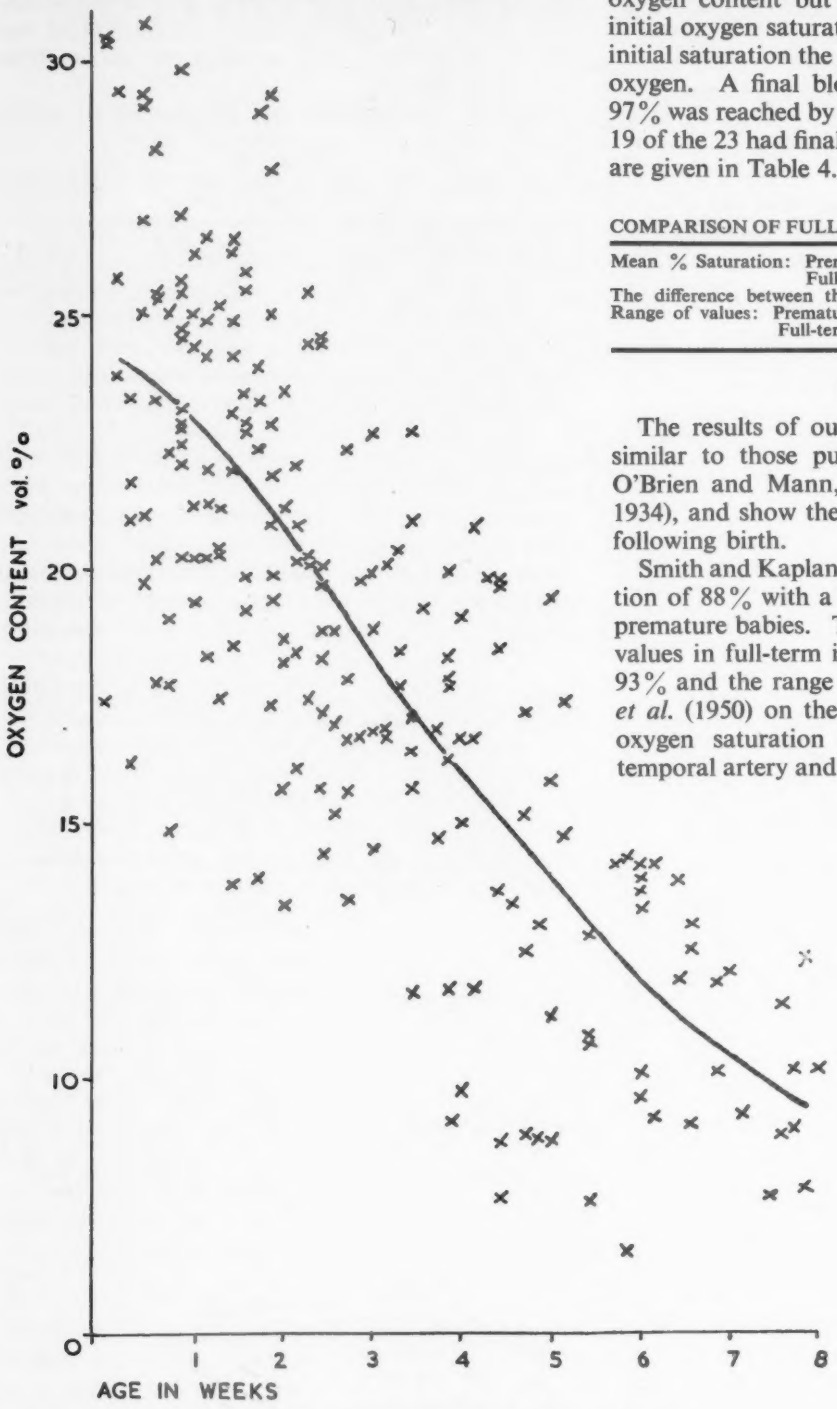

FIG. 2.—Individual blood oxygen values and average curve.

Discussion

The results of our haemoglobin estimations are similar to those published by others (Arthurton, O'Brien and Mann, 1954; Merrit and Davidson, 1934), and show the expected fall in the few weeks following birth.

Smith and Kaplan (1942) found an average saturation of 88% with a range from 75% to 99% in 23 premature babies. These authors also found higher values in full-term infants, their mean result being 93% and the range from 82% to 100%. Graham *et al.* (1950) on the other hand found the average oxygen saturation of blood obtained from the temporal artery and as determined by the Van Slyke method to be 93%. In their investigation the younger premature infants (1-14 days) gave essentially the same results as the older group (14-65 days). Jonxis (1953), using a photoelectric apparatus, found that 'in nearly all examined mature and premature infants the oxygen saturation is on the same level as that of adults, viz., 97%, but he also states that greater variations occur in premature infants.

Graham *et al.* (1950) report that on placing premature infants in an atmosphere of 70 to 79% oxygen the average arterial saturation rose from 93% to 100%, and in an atmosphere of 80% to

TABLE 4

EFFECT OF OXYGEN ADMINISTRATION ON BLOOD OXYGEN CONTENT AND OXYGEN SATURATION

Oxygen Saturation (%)			Oxygen Content (vol. %)			
Before Oxygen	Increase	After Oxygen	Before Oxygen	Increase	After Oxygen	
64·5	15·5	80·0	7·7	2·4	10·1	
66·0	32·5	98·3	17·8	11·2	26·6	Av. inc. O_2 content = 4·3
66·4	11·8	78·2	9·1	1·6	10·7	Av. inc. O_2 satn = 18·45
74·0	14·2	88·2	10·1	1·9	11·9	
80·0	9·7	89·7	14·7	1·8	16·5	
83·4	12·9	96·2	22·4	3·5	25·9	
84·0	9·6	93·6	15·2	1·7	16·9	Av. inc. O_2 content = 2·7
84·0	13·4	97·4	18·4	2·9	21·3	Av. inc. O_2 satn = 11·9
87·3	10·7	96·0	24·6	2·4	27·0	
88·3	11·7	100·0	11·9	1·6	13·5	
89·5	15·5	105·0	27·0	4·8	31·8	
90·1	3·2	93·3	10·9	1·5	11·4	
90·5	3·7	94·2	20·1	0·6	20·7	
91·0	7·0	98·0	22·4	1·8	24·2	
92·0	11·0	103·0	21·5	2·5	24·0	
92·2	0	92·2	11·5	0	11·5	Av. inc. O_2 content = 1·3
92·4	7·6	100·0	24·2	1·9	26·1	Av. inc. O_2 satn = 5·3
92·6	11·0	103·6	25·6	3·0	28·6	
93·0	8·0	101·0	20·0	1·7	21·7	
94·4	0	94·4	23·3	0	23·3	
95·3	2·9	98·2	19·9	1·6	20·5	
100·0	4·0	104·0	19·8	0·8	20·6	

89% oxygen there was a further rise to 102%, Prec and Cassels (1952) exposed 14 full-term infants aged 3½ days to an atmosphere of 90% oxygen and found that the average blood oxygen saturation rose from 93·6% to 100%. In the present series the average blood oxygen saturation was 88% with a range from 61·5% to 102%. An increase in the oxygen content and saturation of the blood occurred in nearly all our cases when oxygen was administered. The rise was not so great as that obtained by other workers but we never gave a higher concentration than 60%.

These findings support the view that the blood of the premature baby has at most times a lower oxygen saturation than the full-term baby or adult and that this saturation can be increased by giving oxygen.

The progress of all our babies was quite satisfactory during the period that they were being studied with regard to weight gain, temperature and general behaviour. With the exception of one infant who had a cyanotic congenital heart lesion, none showed cyanosis or any respiratory distress. Chest radiographs of three whose blood oxygen saturation fell below 70% on

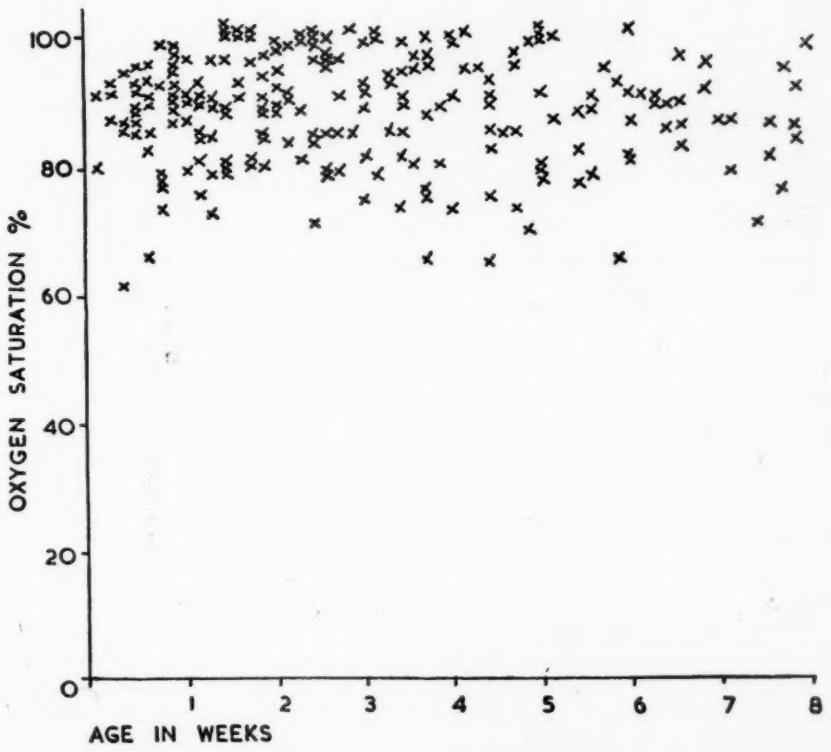

FIG. 3.—Percentage oxygen saturation.

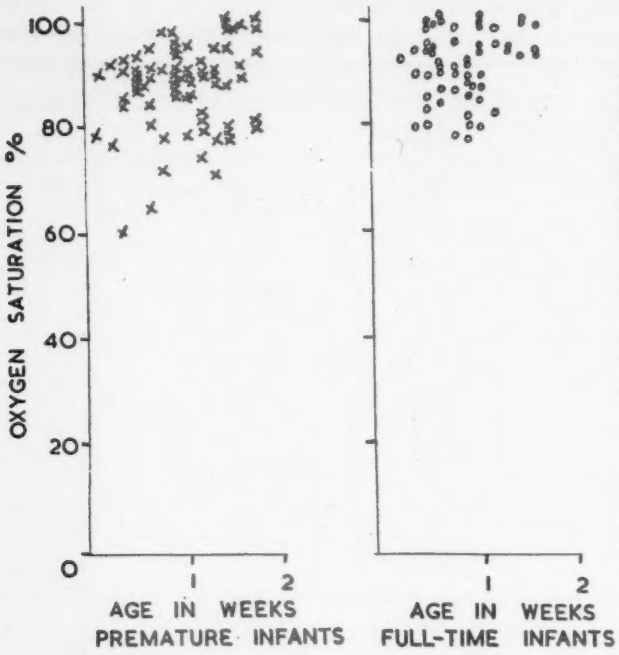

FIG. 4.—Percentage oxygen saturation of premature and full-term infants during the first two weeks of life.

three or more occasions revealed normal lung fields and a normal cardiac outline. It seemed to us that the progress of these babies is unlikely to have been improved by the prolonged administration of oxygen.

The high blood oxygen content, as opposed to the percentage saturation, that was found in the first few days of life when the haemoglobin was high, is worthy of note. In a number of cases it was over 25 vol. %. With oxygen administration and a high haemoglobin it would not be difficult to reach figures over 30 vol. %.

Summary

The blood oxygen saturations of 40 premature babies were determined on 238 occasions between birth and 3 months by a microgasometric method. The mean value was 88·8% in comparison with 93% for full-term infants. The administration of oxygen resulted in a rise in the blood oxygen content and saturation on 21 of the 23 times that it was given. There was, however, no indication that prolonged oxygen therapy was needed by any of the infants at the time they were being studied. It is unlikely that the routine study of blood oxygen levels of healthy premature babies would assist in their general management.

We are grateful to Dr. E. Sherwood Jones, now in the Department of Medicine, and to members of the Liverpool School of Tropical Medicine for their guidance when we were learning the technique of microgasometric analysis, and to Mr. J. Ireland for preparing the chemicals and giving assistance in the calibration of pipettes.

Dr. P. M. Russell held the Ridgway Fellowship in Paediatrics of the University of Liverpool while conducting this work which formed the basis for a thesis accepted by the University for the degree of M.D.

REFERENCES

Arthurton, M., O'Brien, D. and Mann, T. (1954). *Archives of Disease in Childhood*, **29**, 38.
Graham, B. D., Reardon, H. S., Wilson, J. L., Tsao, M. U. and Baumann, M. L. (1950). *Pediatrics*, **6**, 55.
Hüfner, G. (1894). *Arch. Anat. Physiol. (Lpz.)*, [Physiol. Abt.], p. 130.
Hultgren, H. N. and Hackett, A. J. (1950). *Pediatrics*, **6**, 93.
Jonxis, J. H. P. (1953). In *Anoxia of the Newborn Infant: a Symposium organized by the Council for International Organizations of Medical Sciences*, p. 127. Oxford.
Lundsgaard, C. and Möller, E. (1922). *J. exp. Med.*, **36**, 559.
Malm, E. (1953). In *Anoxia of the Newborn Infant, a Symposium*, p. 195.
Merritt, K. K. and Davidson, L. T. (1934). *Amer. J. Dis. Child.*, **47**, 261.
Prec, K. J. and Cassels, D. E. (1952). *Pediatrics*, **9**, 756.
Roughton, F. J. W. and Scholander, P. F. (1943). *J. biol. Chem.* **148**, 541.
Smith, C. A. and Kaplan, E. (1942). *Amer. J. Dis. Child.*, **64**, 843.
Taylor, E. S. (1954). **Pediat. Clin. N. Amer.**, August, p. 587.
Wilson, J. L., Long, S. and Howard, P. J. (1942). *Amer. J. Dis. Child.*, **63**, 1080.

LOW OXYGEN TENSION IN THE MANAGEMENT OF NEWBORN INFANTS*

BY

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(RECEIVED FOR PUBLICATION MAY 10, 1957)

Prolonged administration of oxygen in high concentrations to premature infants is now being abandoned in most countries, thanks to the studies on retrolental fibroplasia which have shown its harmful effects on the eyes. These studies have led to a revision of the indications for oxygen therapy and prompted renewed interest in its physiological bases in the neonatal period (Engle and Levine, 1955).

It is well known that the arterial oxygen tension is extremely low during intra-uterine life—a condition described by Barcroft as 'Mount Everest in Utero' (Eastman, 1954). Immediately after birth, the arterial oxygen tension increases to the same value as that of the adult, *i.e.*, 100 mm. Hg (Taylor, Govan and Scott, 1951). If the oxygen tension before birth is abnormally low as in asphyxiated infants (Eastman, 1936; Wilson, Torrey and Johnson, 1937; Rooth and Sjöstedt, 1955; Montgomery, Brandfass and First, 1956) or infants delivered by caesarean section (Eastman, 1936; Smith, 1939; Watts, Henderson, Kaump and Davis, 1951; Rooth and Sjöstedt, 1955), this increase will be more pronounced. These changes in the oxygen tension are known to produce important vasomotor reactions in the vessels of the brain, eyes and lungs, which in human infants are of special interest, due to the correlation between the two diseases retrolental fibroplasia and hyaline membrane and oxygen therapy. The frequent coexistence of retrolental fibroplasia and cerebral palsy as shown in the papers by Ingram and Kerr (1954) and Krause (1955) may perhaps also justify relating cerebral palsy to oxygen therapy.

It has been shown in man that an increase in oxygen tension causes a constriction and a decrease a dilatation of the retinal vessels (Cusik, Benson and Boothby, 1940), and these reactions have been studied in relation to retrolental fibroplasia (Huggert, 1952, 1953, 1954 and others). In the human brain the effect of changes in oxygen tension are the same (Tinel, 1927; Cobb and Fremont-Smith, 1931; Kety and Schmidt, 1948; Novack, Shenkin, Bortin, Goluboff, Soffe, Batson and Golden, 1953; Edstrom and Essex, 1956, and others). The vessels of the lungs seem to react in the opposite way to those of the brain and the retina (Ohlsson, 1947; Siebens, Smith and Storey, 1955; Hertz, 1956). Experimental and clinical studies also support the assumption that vascular reactions are of importance in the production of hyaline membrane disease (Tran Dinh De and Anderson, 1954; Bruns and Shields, 1954; Rogers and Gruenwald, 1956). If the infant is asphyxiated before birth the increase in oxygen tension after birth in room air may give an increased vascular response and produce manifestations of disease. Moreover the premature infant is abruptly prevented from spending another one or two months in the uterus at a very low oxygen tension. Its enzyme system is immature and its vessels are less resistant to the strain of the vasomotor reactions caused by the sudden increase in the oxygen tension. This is shown by the very strong correlation between prematurity and retrolental fibroplasia and hyaline membrane disease.

On the basis of these considerations it seems logical to keep premature and asphyxiated infants in an atmosphere of lower oxygen content for some time, perhaps for a period corresponding to full term (Rooth and Sjöstedt, 1954 (cited by Rooth and Sjöstedt, 1956)). Then their first weeks after birth will bear some resemblance to their interrupted intra-uterine life.

Knowing how well newborn infants tolerate extreme hypoxia, we considered that an oxygen tension of 115 mm. of mercury in the ambient air should not involve undue risks. This tension has already been employed in respiratory studies in infants, but only for a short time (Cross and Oppé, 1953; Jonxis, 1953; Miller and Smull, 1955).

* Based on a paper read before the VIIIth International Congress of Pediatrics in Copenhagen, July 24, 1956.

Before starting the treatment of infants with low oxygen tension, we studied its effect on animals. For a period of time varying from one to 40 days, more than 200 newborn rats were continuously kept in airtight cages with a mixture of 15% oxygen and 85% nitrogen. There was no increased mortality among these young rats and the results were so encouraging that we felt justified in beginning to extend the treatment of infants over long periods. Some results of the animal experiments are published (Rooth and Sjöstedt, 1957).

Technique

The infants were kept in ordinary incubators. The desired oxygen concentration was obtained by blowing a mixture of 15% oxygen and 85% nitrogen at a rate of 5 litres/min. through the incubator. The oxygen tension within the incubator was controlled regularly with a Beckman D oxygen analyser.

During the first months of the study, the temperature in the incubator was 25° to 27° C. but was later reduced to 23° to 25° C. The relative humidity was maintained at about 75%. The infants were brought out into room air for feeding and nursing, but otherwise they were kept continuously in the atmosphere of 15% oxygen. Recently we have started to feed the infants by a continuous milk drip via an indwelling naso-gastric tube. The infants are now in the incubators at least 23 hours a day.

Material

At present 33 infants have been treated; 21 of these were delivered at full term, and 12 were premature. The premature infants weighed between 520 and 2,200 g. at birth, and some were asphyxiated at birth.

The infants treated can be divided into three groups:

(1) Fifteen healthy full-term infants treated with 15% oxygen for one to three hours. These infants were the first we treated in order to acquire experience and to measure their arterial oxygen saturation during the treatment. The infants were from 1 to 5 days old when placed in the incubator.

(2) Six other full-term infants, healthy or asphyxiated, were treated for a period up to seven days. The infants were placed in the incubator immediately after birth or after resuscitation.

(3) Twelve premature infants were treated for a period up to five weeks. These infants were also placed in the incubator immediately after birth or after resuscitation.

On two occasions the smaller one of two premature twins was placed in the incubator whereas the other twin was treated in room air and at room temperature.

During the infants' stay in the incubator, analyses were made of the blood and urine, and the heart rate and respiration rate were registered. The vessels of the retina were inspected by ophthalmoscopy. The results of these studies will be reported later in detail. In this preliminary paper we will only draw attention to a few points.

Results

When a full-term infant aged 1 to 5 days is placed in an incubator containing 15% oxygen, it may be a little dyspnoeic and a little cyanotic during the first few minutes. After that it reassumes a normal appearance and usually falls asleep. The infant's arterial oxygen saturation was measured with a Millikan oxymeter, the earpiece of which had been slightly altered in order to fit the ear of the child. The oxymeter was preset at 95% saturation when the infant was breathing air. When exposed to 15% oxygen the arterial oxygen saturation of the infant falls by about 10%. In all cases the value lies between 80 and 90% and remains at the same level. Only when the children start crying does the oxygen saturation increase a little. The results of these analyses were most uniform and a typical finding is given in Fig. 1.

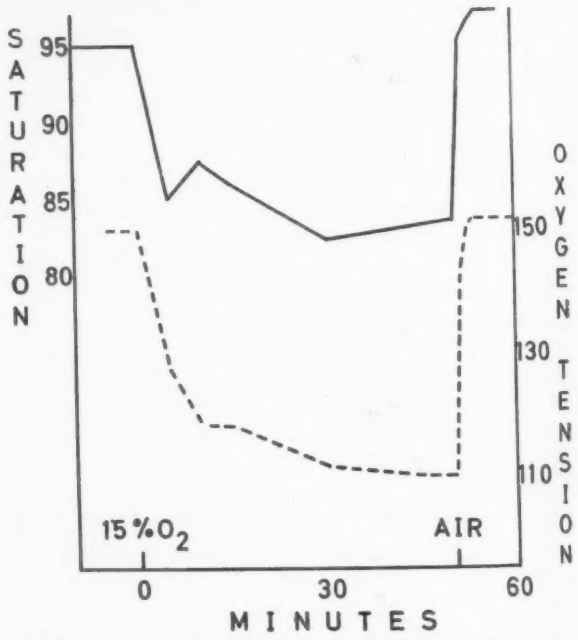

FIG. 1.—Arterial oxygen saturation and oxygen tension in incubator during treatment with 15% oxygen. Arterial oxygen saturation in per cent. Oxygen tension in incubator in mm. of mercury.

A newborn full-term infant exposed to 15% oxygen does not become cyanotic and has no respiratory difficulties. If it is cyanotic when put into the incubator, cyanosis soon disappears and the infant assumes a healthy pink colour. Breathing is deep and quiet and dyspnoea does not occur. In some respects these children, when treated for a few days in 15% oxygen, behave like normal but older children. They are in excellent condition with fairly deep breathing and distinct bradycardia.

Their pulse rate is 100 to 110, their temperature is a little lower than normal, and no side-effects are observed.

In the main premature infants behave like the full-term infants. They are often a little cyanotic and, like other premature infants, during the first few days they have attacks of cyanosis and dyspnoea, but not more often than is usual. In fact, if anything cyanosis and dyspnoea occur more rarely. Their temperature lies between 33° C. and 36° C. for one or two weeks and after that it is normal. These premature infants are also in excellent condition and no side-effects have been observed. Two examples are given in Figs. 2 and 3.

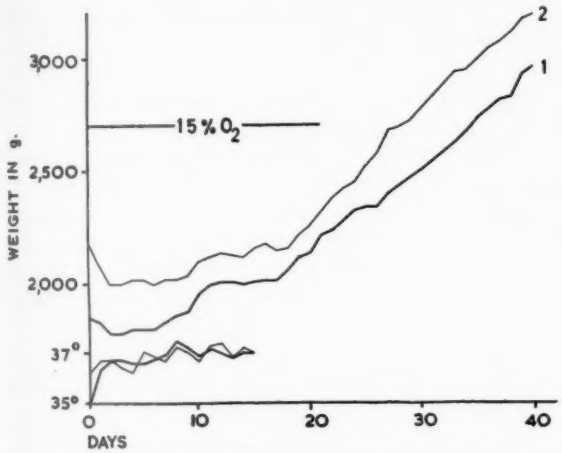

FIG. 2.—Healthy 29-year-old 5-para. Last menstrual period December 16. On August 2 the membranes ruptured and four days later delivery of dichorial twins. Girl 1 spontaneous delivery in o.a. presentation. Weight 1,850 g., length 43 cm. Girl 2 born after version and extraction. Weight 2,180 g., length 49 cm. Girl 1 in incubator, girl 2 in room air. During treatment girl 1 in better condition than her sister. Re-examination after three and six months showed normal development and normal retinal vessels in both infants.

Three of the infants treated have died. Their case histories are given below.

Case Histories

Case 1. Healthy 26-year-old primipara. Normal delivery of 520 g. infant at 22 weeks who lived 19 hours in the incubator with 15% oxygen. At necropsy, the lungs were well aerated and nothing pathological could be seen.

Case 2. Twenty-three-year-old primipara with diabetes and nephropathy since childhood developed gross oedema, proteinuria and raised blood pressure and diabetic retinopathy during pregnancy. Infant born by caesarean section at 28th week and lived six hours in poor condition. At necropsy, intraperitoneal haemorrhage from the umbilical vessels.

Case 3. Thirty-nine-year-old primipara developed antepartum bleeding from first degree placenta praevia at sixth month and bled continuously until delivery at 34 weeks. The infant weighed 2,080 g. and had signs of intracranial haemorrhage with feeble cry and intermittent attacks of cyanosis. It died after nine hours. At necropsy, intracerebral and intraventricular haemorrhage.

These case histories show that the prognosis of these three infants was already grave at birth and that the outcome was not affected by the treatment We do not feel that the fatal outcome in these cases invalidates the favourable experience in the other cases.

Our material is too limited to tell whether there is

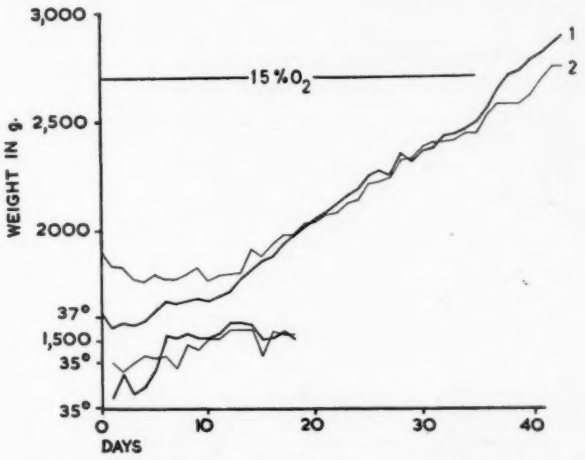

FIG. 3.—Healthy 27-year-old primipara. Last menstrual period May 20. The membranes ruptured January 6 and delivery of dichorial twins next day. Girl 1 spontaneous delivery in o.a. presentation. Weight 1,620 g., length 40 cm. Girl 2 born after version and extraction. Weight 1,900 g., length 41 cm. Girl 1 in incubator, girl 2 in room air. Girl 1 in better condition during treatment than her sister and doubled her weight in seven weeks. Re-examination after three months showed normal development and normal retinal vessels in both infants.

a greater survival rate with this treatment or fewer cases of retrolental fibroplasia, hyaline membrane disease or cerebral palsy. However, the most striking advantage so far has been the favourable general condition of these infants during the treatment. In the two sets of twins which we have observed (Figs. 2 and 3) each twin kept in 15% oxygen was in a markedly better condition than their sisters kept in room air. The treated infants seem to become more advanced and behave like normal older children. Our experience encourages us to continue treating asphyxiated and premature infants with 15% oxygen.

Summary

Twenty-one full-term infants and 12 premature infants were treated in low oxygen tension—15%

oxygen and 85% nitrogen—up to five weeks continuously. There seems to be no risk in the treatment and the treated infants are in an excellent condition.

References

Bruns, P. D. and Shields, L. V. (1954). *Amer. J. Obstet Gynec.*, **67**, 1224.

Cobb, S. and Fremont-Smith, F. (1931). *Arch. Neurol. Psychiat. (Chicago)*, **26**, 731.

Cross, K. W. and Oppé, T. E. (1953). In *Anoxia of the New-born Infant, A Symposium Organized by the Council for International Organizations of Medical Sciences*, pp. 143-156. Oxford.

Cusick, P. L., Benson, O. O. and Boothby, W. M. (1940). *Proc. Mayo Clin.*, **15**, 500.

Eastman, N. J. (1936). *Amer. J. Obstet. Gynec.*, **31**, 563.

—— (1954). *Ibid.*, **67**, 701.

Edstrom, R. F. S. and Essex, H. E. (1956). *Neurology*, **6**, 118.

Engle, M. A. and Levine, S. Z. (1955). *A.M.A. J. Dis. Child.* **89**, 316.

Hertz, C. W. (1956). *Klin. Wschr.*, **34**, 472.

Huggert, A. H. (1952). *Acta paediat. (Uppsala)*, **41**, 463.

—— (1953). *Ibid.*, **42**, 147.

—— (1954). *Ibid.*, **43**, 327.

Ingram, T. T. S. and Kerr, J. D. (1954). *Archives of Disease in Childhood*, **29**, 282.

Jonxis, J. (1953). In *Anoxia of the New-born Infant, A Symposium Organized by the Council for International Organizations of Medical Sciences*, pp. 127-134. Oxford.

Kety, S. S. and Schmidt, C. F. (1948). *J. clin. Invest.*, **27**, 484.

Krause, A. C. (1955). *A.M.A. Arch. Ophthal.*, **53**, 522.

Miller, H. C. and Smull, N. W. (1955). *Pediatrics*, **16**, 93.

Montgomery, T. L., Brandfass, R. T. and First, H. E. (1956). *Amer. J. Obstet. Gynec.*, **71**, 1.

Novack, P., Shenkin, H. A., Bortin, L., Goluboff, B., Soffe, A. M., Batson, P. and Golden, D. (1953). *J. clin. Invest.*, **32**, 696.

Ohlsson, W. T. L. (1947). *Acta med.scand.*, Suppl. 190.

Rogers, W. S. and Gruenwald, P. (1956). *Amer. J. Obstet. Gynec.*, **71**, 9.

Rooth, G. and Sjöstedt, S. (1954). Cited by Rooth and Sjöstedt (1956).

——, —— (1955). *Acta obstet. gynec. scand.*, **34**, 442.

——, —— (1956). *Nord. Med.*, **56**, 992.

——, —— (1957). *Scand. J. clin. Lab. Invest.*, **9**, 174.

Siebens, A. A., Smith, R. E. and Storey, C. F. (1955). *Amer. J. Physiol.*, **180**, 428.

Taylor, E. S., Govan, C. D. and Scott, W. C. (1951). *Amer. J. Obstet. Gynec.*, **61**, 840.

Tinel, J. (1927). *C.R. Soc. Biol. (Paris)*, **96**, 665.

Tran Dinh De and Anderson, G. W. (1954). *Amer. J. Obstet. Gynec.*, **68**, 1557.

Watts, J., Henderson, H., Kaump, D. H. and Davis, R. M. (1951) *Ibid.*, **61**, 1025.

Wilson, R. A., Torrey, M. A. and Johnson, K. S. (1937). *Surg. Gynec. Obstet.*, **65**, 601.

AMINO-ACIDURIA AND HYPERMETABOLISM IN PROGERIA

BY

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In 1886 Hutchinson described the first case of alopecia totalis congenita associated with atrophy of the skin, and in 1904 Gilford reported a similar case and described it as premature senility (senilitas praecox) or progeria. From that time to the present about 20 cases have been described in the world literature (Curtin and Kotzen, 1929; Talbot, Butler, Pratt, MacLachlan and Tannheimer, 1945; Plunkett, Sawtelle and Hamblen, 1954).

Up to the present time the diagnosis has been based, in the absence of any constant biochemical findings, upon the strange external appearance which is constant and recurs in all these cases. We are presenting the following case mainly because several results were obtained during the clinical and laboratory investigations that could be used to explain some of the features of this illness.

Case Report

The patient was a boy of 5½ years, born of parents from Rumania. Both parents were healthy and unrelated. The child was born several months after the parents arrived in Israel. Until the age of about 8 months he developed normally, gained weight satisfactorily and showed no signs of any ailment. He sat up at the age of 7 months and walked at the age of 11 months. His mental development was also within normal limits. He began to talk at the age of 13 months and was a bright, pleasant infant, playing with his parents and the children of their neighbours.

The only thing that appeared somewhat strange to the parents was the absence of hair, a somewhat large head, and perhaps the fact that his first tooth was rather delayed, appearing only at the age of 10 months. At this time the signs of his present illness began to appear: he ceased to gain in weight, the few hairs that he had fell out, his round infantile features became thinner and sharper, and the whole of his head became bird-like.

After several consultations his illness was diagnosed as progeria and numerous therapeutic experiments were without avail: he received vitamins, calcium and even D.O.C.A. for several weeks without any effect. When he was treated with A.C.T.H., however, he gained 2½ kg. in weight and also grew 2 cm. in height; but even these effects were temporary, if indeed we can attribute the slight gain in height and weight to this drug. Eventually, he was sent for consultation to a neurosurgeon* and we were requested by him to take part in the metabolic and endocrinological investigations of the patient.

When he was admitted to hospital he weighed 9·680 kg. His appearance was typical of 'classical' progeria. His nose was sharp and bent, and the bones of the cheeks and chin were small compared with the bones of the forehead. His height was 90 cm. His body build was symmetrical although dwarfed and the skin was thin, particularly on the head, with prominence of the venous pattern. On the body the skin was dry with a faint golden-brown pigmentation in small spots. He had no hair at all; the head was relatively large with prominent eyes partly due to shallow orbital fossae and partly to actual exophthalmos. His teeth were very bad. Fundi and perimetry were normal. No cataracts were noted, and we were unable to feel the thyroid gland with certainty. The chest was narrow but the heart and lungs were within normal limits. The abdomen was protuberant but we were unable to feel the liver or the spleen. The genitals were perhaps slightly larger than the normal for his age and the testicles were in the normal position. The limbs were without pathological findings except for mild flat feet and small and narrow nails. The muscles were weak and poorly developed. The reflexes were normal and he had an unusually high and nasal voice. The E.C.G., E.E.G. and radiographs were all normal.

Intelligence testing was done. The child was lively and able to orientate himself accurately. He took part in conversation and seemed to prefer the company of adults, although the operative intelligence appeared limited in several directions and functions.

Laboratory Investigation. There were two groups of abnormal findings: (1) the excretion of amino-acids and (2) increased metabolic activity.

The amino-acids concentrations were low in the blood (4·8 mg. % as against a normal finding of 6 to 8 mg. %) and increased in the urine.

The amino-acid excretion in the urine was examined by ascending paper chromatography. One-dimensional

* The examination was carried out by Dr. Askenasy at the Beilinson Hospital and we are indebted to him for his courtesy in transferring the child to us.

chromatography was carried out in a butanol : acetic acid: water (11:3:4) solvent, two-dimensional examinations were developed in 3 parts isopropanol: 1% sodium chloride solution containing 1 part 0·5% urea and 80% phenol solution containing 0·1% 8 hydroxyquinoline.

Several examinations were carried out (testing always a 1/40,000 part of a 24-hour urine collection) and a marked amino-aciduria was always detected. The pattern of increased excretion was not constant; in some samples a general amino-aciduria was found (glycine, serine, lysine, arginine, alanine, histidine, taurine, threonine) while on other days only one or two acids were excreted in great excess (histidine, or glutamine and lysine).

A semi-quantitative examination was carried out by a method adapted from Smith and Tompsett (1954). A one-dimensional chromatogram of the urine was divided into 10 equal strips corresponding to increasing R_f values. The amino-acids were eluted into a buffered ninhydrin solution and the colours resulting read in a spectrophotometer. The results of the readings were computed from a standard curve prepared with glycine as the reference acid and plotted on graph paper against the corresponding R_f values. An example of such an examination of the patient's urine is given in Fig. 1, showing a general amino-aciduria.

The blood amino-acids were examined by the sodium-beta-naphtoquinone method (Kolmer and Boerner, 1945) and were found to be lowered: whole-blood amino-acids 4·8 mg. % (normal 6-8) and serum-amino-acids 2·9 mg. % (normal 4-6).

In addition to the finding of alterations in the levels of the amino-acids only one other finding was obvious and that was the result of the test with radioactive iodine which showed increased absorption of the iodine by the thyroid gland. This finding was confirmed also by the P.B.I. and B.M.R. (Fig. 2).

The treatment was prescribed in accordance with the pathological findings and the child was given propylthiouracil, 50 mg. daily, and methyltestosterone, 50 mg. daily. On this therapy he gained more than 3·400 kg. in two months (from 9·600 kg. to 13 kg.) and grew approximately 4 cm. His appearance was otherwise unchanged and there was also no effect whatsoever on the amino-aciduria. The attempt to influence the alopecia with cortisone and A.C.T.H. also failed.

Discussion

Amino-aciduria can be caused by three mechanisms. (1) Overflow, which is when the amino-acid level in blood increases as the result of result of a liver necrosis, extensive muscular atrophies, hyperthyroidism, increased protein catabolism in wasting diseases and other causes, and an excessive amount of amino-acid is excreted in urine as a result. In our patient the amino-acid levels in

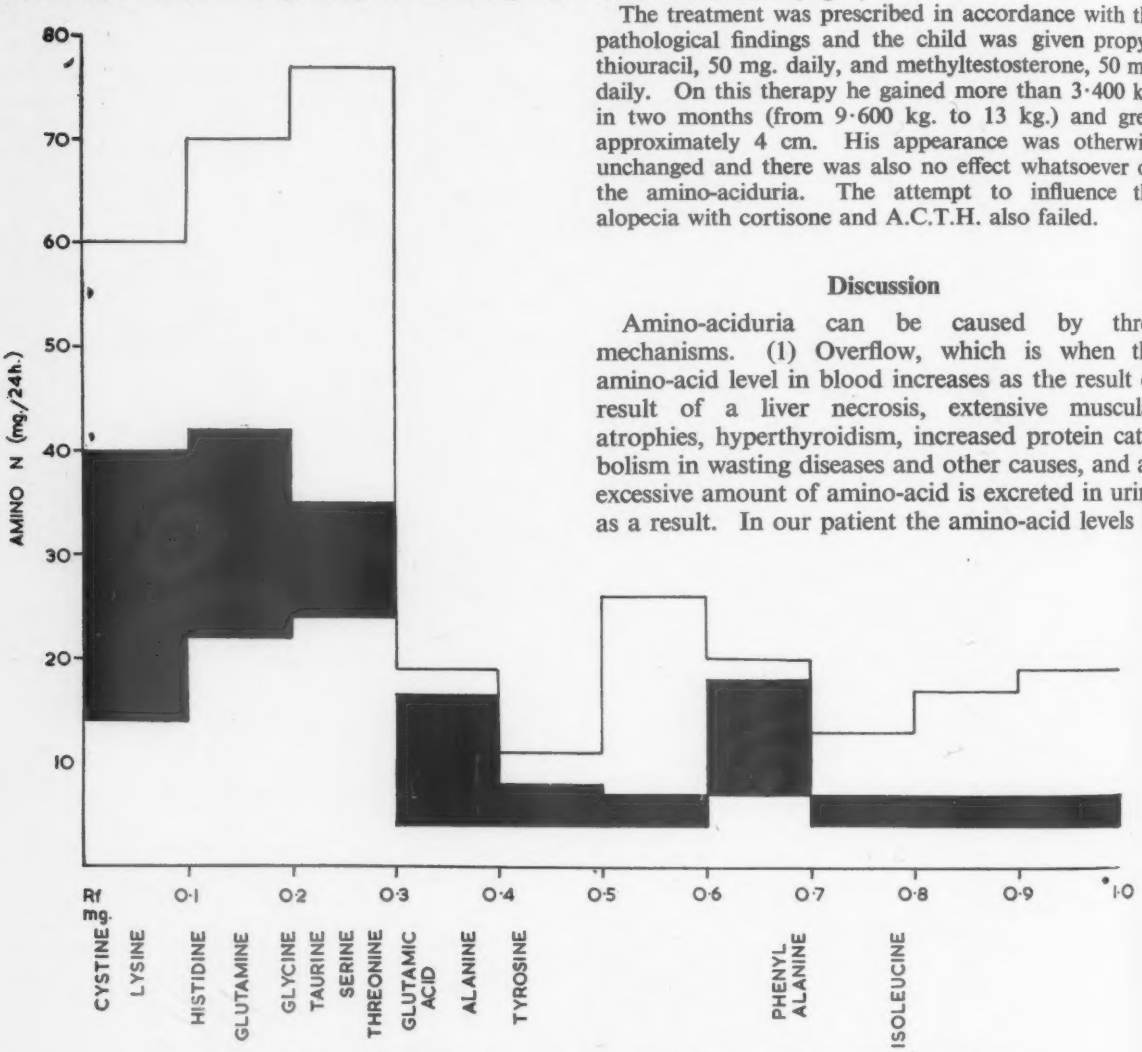

FIG. 1.—Amino-acid excretion in the urine of the patient (the shaded area represents normal excretion).

blood never exceeded the normal limits. We were therefore able to exclude overflow as the explanation.

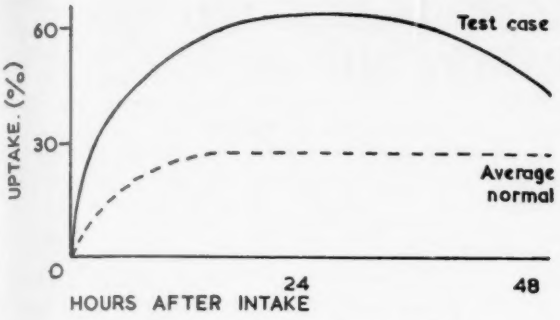

FIG. 2.—Results of thyroid function tests.

(2) Widespread renal damage, in which amino-aciduria is accompanied by other signs of renal disorder, such as haematuria, pyuria, or albuminuria, but none of these signs was found in our patient.

(3) Primary amino-aciduria of the type found in the de Toni-Fanconi syndrome, hepatolenticular degeneration or cystinuria, in which disorders the amino-aciduria is probably caused by specific tubular damage, interfering with normal reabsorption of some substances without giving rise to general kidney damage and without any rise of amino-acid concentration in the blood.

FIG. 3.

The finding of a constant amino-aciduria accompanied by a low blood amino-acid level seems to indicate a defect similar to that of the de Toni-Fanconi type in our case of progeria.

We also tried to localize the site of hypermetabolism in our case. In general, it is not thought that the thyroid gland plays any part in the pathogenesis of the hypermetabolism in progeria. In our patient the rapid and increased absorption of the radioactive iodine would have suggested that the thyroid gland was over-active, causing the increased metabolism (Talbot *et al.*, 1945).

Summary

A case of progeria is described in a boy aged 6½ years. The main biochemical findings were (1) hypoaminoacidaemia, (2) hyperaminoaciduria, (3) increased I_{131} thyroid uptake, (4) high P.B.I. values in blood.

It is suggested that the disease may be related to the de Toni-Fanconi group.

Appendix

In consultation with Professor Gaillard (Leyden) we tried to ascertain whether there were any constituents that could shorten the life span of the cells in the patient's serum. With the help of the Medical School, Jerusalem, the blood of the patient was examined for haemolysins and leucocytins. These, however, were absent. We were therefore unable to postulate increased destruction of leucocytes or erythrocytes. The leucocytes were kept alive *in vitro* for 49 hours at a temperature of 6° C. and they did not differ from normal leucocytes.

We also tested the phagocytosis of the leucocytes of standard *Staph. aureus* organisms compared with leucocytes of normal blood and no difference was found. Transfer of the patient's leucocytes to normal plasma and also transfer of the child's plasma to normal blood showed no deviation from the normal; the phagocytes developed normally.

REFERENCES

Curtin, V. T. and Kotzen, H. F. (1929). *Amer. J. Dis. Child.*, 38, 993.
Gilford, H. (1904). *Practitioner*, 73, 188.
Hutchinson, J. (1886). *Med.-chir. Trans.*, 69, 473. As cited in Plunkett *et al.* (1954).
Kolmer, J. A. and Boerner, F. (1945). *Approved Laboratory Technic*, 4th ed. New York and London.
Plunkett, E. R., Sawtelle, W. E. and Hamblen, E. C. (1954). *J. clin. Endocr.*, 14, 735.
Smith, D. C. and Tompsett, S. L. (1954). *J. clin. Path.*, 7, 79.
Talbot, N. B., Butler, A. M., Pratt, E. L., MacLachlan, E. A. and Tannheimer, J. (1945). *Amer. J. Dis. Child.*, 69 267.

THE APPLICATIONS OF SERUM LIPOPROTEIN ELECTROPHORESIS IN PAEDIATRIC PRACTICE

BY

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In the investigation of many metabolic disorders of childhood, a study of the serum lipids and lipoproteins is important. Serum protein electrophoresis has become an everyday tool in most laboratories; lipoprotein electrophoresis has not yet attained such acceptance, though its research value is becoming recognized.

Studnitz (1955) studied the normal lipoprotein values in pregnancy and Rafstedt (1955) those in infancy and childhood. Other recent publications include surveys of lipoprotein investigations in various diseases that involve lipid metabolism (Adlersberg, Bossak, Sher and Sobotka, 1955; Dangerfield and Smith, 1955) and detailed observations in idiopathic hyperlipaemia and hypercholesterolaemia (Herbst, Lever and Hurley, 1955), atherosclerosis (Gottfried, Pope, Friedman, Akerson and Di Mauro, 1955) and malnutrition (Laurell, 1955).

We have applied a method of lipoprotein electrophoresis to some conditions encountered in paediatric hospital practice and describe here a selection from our results. We have found the method of value in various diseases which involve lipid metabolism both primarily and secondarily.

The main types of serum lipid, apart from minute concentrations of steroids and other compounds of undoubted significance but not to be discussed here, are triglyceride esters usually present as discrete particles, cholesterol and cholesteryl esters held in solution by physical bonding to one or more of the serum proteins, and phospholipids similarly bound to serum proteins.

The process of electrophoretic separation of serum proteins on absorbent paper is readily adapted to the separation of three fractions of serum lipid. Examination of the fractions (Kunkel and Slater, 1952) has shown that alpha lipoprotein consists of alpha globulin combined with phospholipid (66% of the total alpha lipid) and with cholesterol and its esters (33% of the total alpha lipid); and that beta lipoprotein consists of beta globulin combined with phospholipid (44% of the total beta lipid) and with cholesterol and its esters (56% of the total beta lipid). A third component, which we have designated the omega fraction, consists of triglyceride esters in nearly pure state in the form of chylomicron particles. The protein-bound lipids migrate electrophoretically with speeds approximating to those of the globulins concerned, though with certain subtle differences to be discussed later; whereas the omega fraction, because of adsorption to the paper, appears devoid of electrophoretic mobility and remains at or close to the origin of the electrophoretic separation.

In the present study of serum proteins and lipoproteins we have confined ourselves to electrophoretic separations, though of course that technique does not distinguish between the various types of lipid material in the several individual fractions.

Our technique is based on procedures described by Swahn (1952a, 1952b) and by Adlersberg *et al.* (1955), and is described here in detail as we have developed certain modifications; it includes a quantitative assessment of the serum total lipid and its fractions.

METHODS

Venous blood, collected with a silicone- (not paraffin) coated syringe, was allowed to clot and the serum removed after centrifuging for only 5 to 10 minutes at 2,500 r.p.m. to avoid separation of low specific gravity lipids. A minute drop of 10% sodium azide was added as preservative and the serum stored at 4° C. Electrophoresis was performed on the specimens within a few days of collection, as occasionally prolonged storage was found to cause artefacts in the electrophoretic lipid patterns.

The electrophoretic separations were done in a horizontal apparatus similar to that of Grassmann, Hannig and Knedel (1951), using Whatman No. 3 mm. paper and 0·06 m. barbitone buffer at *p*H 8·6. Each paper strip, 13·5 × 2·0 in. (12 in. between the buffer solutions in the reservoirs), was marked in pencil transversely at a point 5 in. from the cathode end; and six such papers when arranged in parallel were conveniently

operated by a current of 12 mA. during an overnight period of about 16 hours.

Before application of the serum, the paper strip was soaked in buffer solution and then firmly blotted. A minute drop of a saturated solution of bromophenol blue (B.D.H. water-soluble indicator) was added to the serum; a volume of 0·15 ml. coloured serum was then pipetted on to the pencilled origin line. A duplicate paper strip was also prepared, and a third in a similar manner but using only 0·05 ml. serum. When a further set of three papers was also ready, all six were placed in the electrophoresis apparatus, and drops of buffer solution were then pipetted asymmetrically on to the ends of the papers to achieve saturation equilibrium. By judicious placing of the drops the serum load was prevented from moving from the origin line. The apparatus was then closed. After waiting 30 minutes or more for vapour equilibrium to become established, the current was applied.

When the albumin-bound bromophenol blue had migrated about 4 in. toward the anode, the electrophoretic separation was discontinued; the papers were removed and dried for 30 minutes at 100° C. One paper, loaded with 0·15 ml. serum, was then prepared for quantitative determination of the separated lipids. To the centre of an unoccupied area of the paper strip near the cathode end (measuring $1\frac{7}{8}$ in. in length) a standard quantity (0·37 mg.) of arachis oil was applied in the form of 0·08 ml. of a solution containing 0·5 ml. arachis oil per 100 ml. solvent (ether-ethanol 1:1). When the solvent had evaporated, the serum lipids and the standard spot were stained by overnight immersion of the paper strip in a freshly prepared saturated solution of oil red O (George T. Gurr, Ltd.) in ethanol-water (60:40). The paper was then washed, first in ethanol-water (60:40) for about half a minute, then in water for about half an hour, after which it was hung in the air until dry.

The paper was then cut transversely into $\frac{3}{8}$ in.-wide segments, of which five comprised the standard spot and 20 the serum lipids including one or more blank segments. Each segment was then placed in a test tube and 6·0 ml. propanolacetic acid mixture (80:20) added to each tube. After standing overnight the concentration of eluted oil red O dye in each of the tubes was determined absorptiometrically using narrow-band light at 525 millimicrons peak wave length.

The extinction values were then plotted as ordinates against linear distance and the serum lipid profile completed (Fig. 1A). The graph was then subdivided into three parts representing the omega fraction and the beta and alpha lipid peaks. Demarcation of the omega fraction from the beta peak was difficult in some cases. Particularly large omega fractions, or their absence, were obvious, but intermediate values sometimes presented merely as a convexity on the cathode slope of the beta peak. In such cases the component curves were extrapolated and the contributory extinction values were carefully allocated to effect a subdivision.

Grouped extinction values were summed to represent the three fractions, and the amounts of the fractions were then calculated by reference to the extinction sum for the standard spot. The resulting values for the alpha, beta and omega lipid fractions and total lipid were thus obtained in terms of their uptake of oil red O relative to the uptake by arachis oil.

The other two electrophoretic paper strips (0·15 and 0·05 ml. serum) were each divided longitudinally; one-half of each was stained with oil red O, and the other half with bromophenol blue to reveal albumin and alpha$_1$, alpha$_2$, beta and gamma globulins, using the aqueous staining reagent and subsequent acid-aqueous washing technique described by Kunkel and Tiselius (1951).

A careful comparison of these stained papers yielded qualitative information about the patterns and the mobility correspondence between the serum lipid fractions and the protein fractions. Qualitative features of the protein pattern were clearer on the lightly loaded paper, and of the lipid pattern on the more heavily loaded paper. As a rule the mobility correspondence of the beta lipoprotein peak was assessed from inspection of the lightly loaded paper, whereas the properties of the more faintly stained alpha lipoprotein band were judged from the more heavily loaded paper. In most cases albumin and the serum globulins were also quantitatively evaluated (Salt, 1956) and in a few selected cases the serum protein profiles were also obtained by detailed (40-part) elution of the bromophenol blue-stained strips.

RESULTS

Normal Findings

Sera from 27 children in whom there was no reason to suspect an abnormality of lipid metabolism were examined. These specimens were not specifically collected for our studies and this accounts for the wide differences in the omega fraction, some specimens having been obtained in the fasting state, others after a meal containing fat.

Although the normal ranges (Table 1) for total

TABLE 1
NORMAL SERUM LIPOPROTEIN VALUES

Age Group	No. of Cases	Mean Concentration and Range (mg. per 100 ml. serum)					
		Total Lipid	Electrophoretically Separated Fractions				Ratio Beta/Alpha
			Omega	Beta	Alpha	Beta+Alpha	
1–6 months	6	492 294–711	41 6–119	285 162–427	166 117–199	451 282–626	1·7 1·3–2·2
½–11 years	21	676 466–860	43 0–105	434 302–576	200 152–283	633 466–815	2·2 1·6–3·0

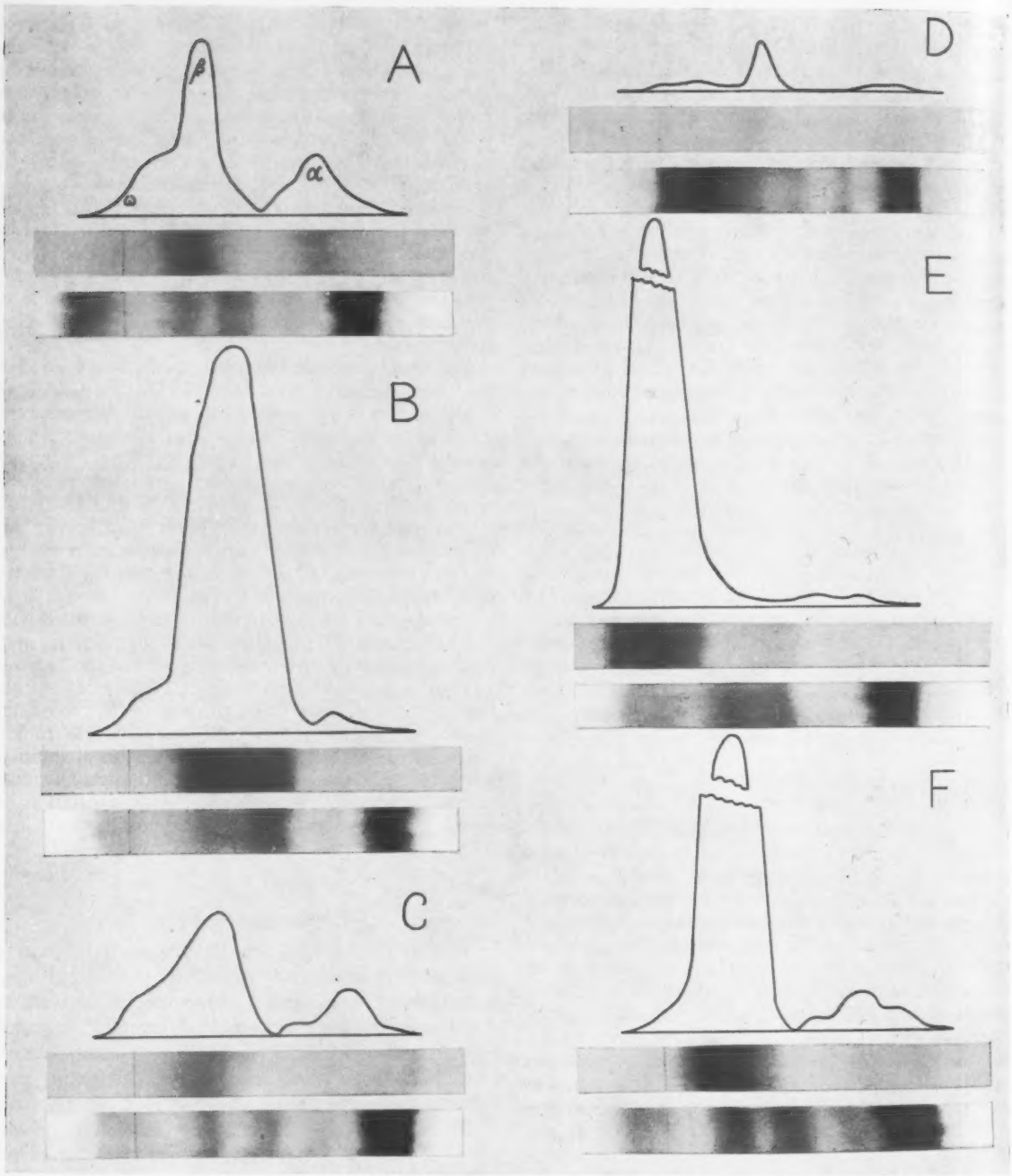

FIG. 1.—Serum lipoprotein electrophoretic patterns (upper strip of each pair, stained with oil red O, and profile superimposed) and serum protein electrophoretic patterns (lower strip of each pair, stained with bromophenol blue). A. Normal (aged 5 years) showing the three lipid fractions. B. Nephrosis. C. Diabetic coma. D. Hepatic cirrhosis. E. Essential hyperlipaemia. F. Essential hypercholesterolaemia.

lipids and for the three separate fractions are wide, the ratio of the beta fraction to the alpha fraction is relatively constant. Fig. 1A shows the normal electrophoretic patterns after staining for proteins and lipoproteins, and the lipid profile obtained by the elution technique.

The positions of the normal lipoprotein bands in relation to the protein bands are characteristic. The stained beta lipoprotein band, which coincides in its position with the beta globulin of the protein-stained strip, has a compact appearance with a sharp leading edge. These characteristics distin-

TABLE 2

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN PATIENTS WITH NEPHROSIS

Patient	Serum Albumin (g./100 ml.)	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Beta LP Peak and character of Beta LP Band*
		Total	Omega	Beta	Alpha		
C.M. (1) ..	0·4	2,036	102	1,893	41	47	A+
R.F.	0·8	1,722	86	1,464	172	8·5	A+
R.N.	1·0	1,348	27	1,159	162	7·2	A+
S.P.	1·3	3,430	103	3,259	68	48	A+
A.H.	1·3	1,691	237	1,387	67	20·5	A
G.M.	1·5	1,610	193	1,240	177	7·0	A+
V.H.	2·2	1,323	79	1,005	239	4·2	N+
C.M. (2) ..	4·0	1,372	137	947	288	3·3	N
J.L.	4·9	907	45	671	191	3·5	N
R.G.	5·2	933	9	681	243	2·8	N

* A indicates advanced position of the peak; N the normal position.
\+ denotes leading edge advanced towards the anode.

guish the normal from many pathological patterns. During the first six months of life, the beta lipoprotein band usually appears less intense and tends to be more widely diffused, though in general the pattern resembles that described for older children.

The stained alpha lipoprotein band is more diffuse than the beta band and corresponds in position with that occupied by alpha$_1$ globulin and the adjacent half of the albumin. In our assessment of the various patterns, normal and pathological, quantitative changes in alpha lipoprotein have been of greater value than qualitative variations in the appearance of the alpha band, though in two instances, described later, the alpha lipoprotein exhibited a striking qualitative abnormality.

Nephrosis

Sera were examined from nine children, aged 2-13 years, at various stages of the disease or in remission. The results are presented in Table 2, arranged according to the concentration of serum albumin. Typically the total lipids were grossly increased owing to a great increase in the beta fraction. The alpha fraction was sometimes decreased and the beta/alpha ratio exceeded the normal.

Fig. 1B shows a typical pattern at the height of the disease. In these cases the beta lipoprotein was seen at an advanced position, sometimes between alpha$_2$ globulin and beta globulin, sometimes even as far as alpha$_2$ globulin, although not infrequently these globulin fractions were imperfectly separated or even merged in a way characteristic of nephrosis. In some instances there was in addition to the beta peak a less distinct fraction extending toward the anode. (Patterns that showed this abnormality are indicated in the tables by (+) and the normal or advanced position of the beta peak by N or A respectively.) As the serum albumin concentration increased, the beta lipoprotein peak returned to its normal position and magnitude, and the alpha lipoprotein fraction increased to a more normal proportion.

Cystine Storage (Lignac-Fanconi) Disease

Four cases were examined; the results are arranged in Table 3 according to the blood urea levels. In Case D.R. the blood urea and the lipoprotein pattern were normal. In the other cases the beta lipoprotein fraction either migrated to an advanced position, or the beta peak appeared at the normal position and a less intensely stained part of the beta fraction was also present extending forward to the alpha$_2$ globulin position. In two

TABLE 3

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN PATIENTS WITH CYSTINE STORAGE (LIGNAC-FANCONI) DISEASE

Patient	Blood Urea (mg./100 ml.)	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Beta LP Peak and Character of Beta LP Band*
		Total	Omega	Beta	Alpha		
P.R. (1) ..	140	1,152	58	876	218	4·0	N+
P.R. (2) ..	109	980	167	715	98	7·3	A
K.C.	90	1,225	110	919	196	4·7	A+
L.S.	52	686	55	480	151	3·2	N+
D.R.	39	665	13	399	253	1·6	N

* See footnote, Table 2.

TABLE 4

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN PATIENTS WITH IDIOPATHIC INFANTILE HYPERCALCAEMIA

Patient and Age in Months	Type of Case	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Beta LP Peak and Character of Beta LP Band*
		Total	Omega	Beta	Alpha		
R.F. 8	Benign	882	62	688	132	5·2	A
L.S. (1) 3	Benign	515	77	402	36	11	A
L.S. (2) 4	Benign	711	199	398	114	3·5	A
M.S. 18	Severe	909	73	554	282	2·0	A
J.S. 6	Severe	1,568	204	1,286	78	16	A+

* See footnote, Table 2.

of the cases (P.R. and K.C.) the total lipid and the beta lipoprotein concentrations were high and the beta/alpha ratio was slightly or moderately raised.

Idiopathic Infantile Hypercalcaemia

Four cases were examined, two (R.F. and L.S.) of the type described by Lightwood (1952) and two of the type described by Fanconi and Girardet (1952) and Schlesinger, Butler and Black (1952). Our results are given in Table 4. In all the cases the beta lipoprotein peak migrated to an advanced position and in three instances the serum total lipids were elevated.

Lipochondrodystrophy (Hurler's Syndrome)

Three patients were examined (Table 5); Case A.L. was studied on four occasions between the ages of 4 and 15 months. The other two patients were brothers (P.W., J.W.) and serum from their unaffected mother (Mrs. D.W.) was also examined. Results from the mother were normal; those of her children, as well as those of Case A.L., all showed a moderately increased beta/alpha ratio, a decreased alpha fraction and a normal or slightly increased beta fraction. This finding is of interest as, to our knowledge, a serum abnormality has not previously been described in this condition.

Mobilization (Transport) Lipaemia

Hypoproteinaemic Oedema (Due to Malnutrition). This boy (Case M.H., Table 6) was admitted at the age of 13 months with generalized oedema due to hypoproteinaemia (serum proteins: total 3·7, albumin 1·9, globulin 1·8 g. per 100 ml.). Since the age of 9 months he had refused most food and steadily lost weight. The first examination of serum lipids was made shortly after admission. The total lipids and beta fraction were high. In the electrophoretic protein strip a fraction was observed which had migrated in advance of the albumin, and in the corresponding position on the strip stained by oil red O a lipid fraction was present. This fraction appeared to be a modified alpha lipoprotein probably possessing an increased mobility as a result of acquisition of extra fatty acid components derived from lipolysis of fat mobilized from the depots. With treatment the boy's condition improved, the serum albumin increased and the oedema cleared. A month later the lipoprotein electrophoresis had returned to normal.

Chylothorax. In this 5-year-old boy (Case C.H.) the chylothorax was the result of a lymphangiomatous malformation of the thoracic duct. For eight weeks enormous volumes of chyle had accumulated in, and were aspirated from, the pleural cavity.

TABLE 5

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN LIPOCHONDRODYSTROPHY (HURLER'S SYNDROME)

Patient	Age	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Beta LP Peak, and Character of Beta LP Band*
		Total	Omega	Beta	Alpha		
A.L.	4 months	882	238	503	141	3·6	N+
„	7 „	760	15	578	167	3·5	N
„	9 „	809	113	575	121	4·7	N
„	15 „	662	40	543	79	6·8	N
P.W.	20 „	662	113	437	112	3·9	N
J.W.	10 years	662	46	483	133	3·7	N
Mrs. D.W.	Mother of P.W., J.W.	760	68	494	198	2·5	N

* See footnote, Table 2.

TABLE 6

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN CONDITIONS WITH MOBILIZATION (TRANSPORT) LIPAEMIA

Patient	Condition	Characteristic Serum Chemistry	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Lipoprotein Peaks and Character of Bands*	
			Total	Omega	Beta	Alpha		Beta	Alpha
M.H. (1)	Malnutrition, oedema, hypoproteinaemia	Albumin 1·9%	1,112	6	912	194	4·7	N+	Pre-albumin
(2)	Improved	Albumin 4·2%	671	67	429	175	2·5	N	N
C.H. (1)	Chylothorax	Albumin 2·1%	1,103	121	805	177	4·6	N+	N
(2)	After successful treatment	Albumin 2·4%	613	25	527	61	8·6	A	N
A.S. (1)	Idiopathic hypoproteinaemia (?hypercatabolic), oedema	Albumin 1·8%	1,250	325	800	125	6·4	A+	N
(2)	Improved	Albumin 3·6%	711	213	320	178	1·8	N	N
M.G. (1)	Diabetes mellitus, in coma ..	Sugar 1,570 mg. %	1,005	151	653	201	3·3	A+	Pre-albumin
(2)	Out of coma	—	613	31	484	98	4·9	A+	N

*See footnote, Table 2.
'Pre-albumin' denotes advanced position of alpha lipoprotein, such that the alpha fraction extends beyond the leading edge of the albumin.

Table 6 shows the findings at this stage of the illness when he had lost approximately 10 lb. in weight, when his general condition was rapidly deteriorating and the serum albumin had fallen to 2·1 g. per 100 ml. The total lipids and the omega and beta fractions were increased. Presumably mobilization of depot fat was the cause of this perplexing finding of pronounced chylomicronaemia in the virtual absence of alimentary chylomicron absorption. Ultimately the condition cleared with deep *x*-ray therapy. Examination of the serum was repeated within a fortnight of the leak of chyle into the pleural cavity having been sealed. The total lipid and the beta and omega fractions had by then returned to normal levels, and the alpha fraction had decreased. It may be speculated that with recovery the mobilization of depot fat had ceased and therefore excessive lipaemia was no longer a feature. The low alpha fraction appearing during convalescence was regarded, in the light of other experience (see below), merely as a non-specific abnormality.

Idiopathic Hypoproteinaemia. This 3-year-old girl (Case A.S.) had developed generalized oedema five days before admission. Investigations suggested that the oedema was due to hypoproteinaemia of hypercatabolic origin (Ulstrom, Smith and Heimlich, 1956; Schwartz and Thomsen, 1957). Table 6 gives the findings shortly after admission when the total lipids and the omega and beta fractions were increased. The beta fraction was in the advanced position, the lipid pattern resembling that seen in nephrosis. On treatment with a protein-supplemented diet she improved rapidly and was discharged after seven weeks, when the serum proteins and lipoproteins were normal except for persistence of a high omega fraction. We regarded this persistent chylomicronaemia as another instance of mobilization lipaemia.

Diabetic Coma. In Case M.G. (see Table 6 and Fig. 1c) the serum total lipids, the omega and beta fractions were high; and the beta lipoprotein band occupied an advanced position. In addition, a fraction of alpha lipid and protein was discernible in the pre-albumin position.

A few days later, when the patient was out of coma but the diabetes still not well controlled, the lipoprotein pattern was more nearly normal, though the beta fraction remained in the advanced position and the alpha fraction, now in the normal position, was low.

Glycogen Storage Disease. We were able to study a family of five siblings of whom two (J.M., S.M.) were affected by the disease with hepatic involvement. The results are given in Table 7, and for comparison the findings in the three normal siblings (G.M., A.M., Ja.M.) are included. In the affected children the total lipid and the beta fraction were increased and the alpha fraction decreased, all in contrast to the normal findings in the unaffected children.

A third and younger case (T.L.), in whom the diagnosis though not proven by liver biopsy was

TABLE 7

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN PATIENTS WITH GLYCOGEN STORAGE DISEASE AND IN UNAFFECTED SIBLINGS

Subject	Age in Years	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Beta LP Peak, and Character of Beta LP Band*
		Total	Omega	Beta	Alpha		
Affected siblings:							
J.M.	5	931	47	745	139	5·3	A+
S.M.	3	1,029	82	854	93	9·2	N+
Unaffected siblings:							
G.M. ..	6	784	55	510	219	2·3	N
A.M.	4	613	37	386	190	2·0	N
Ja.M.	2	441	44	260	137	1·9	N
Another probable case							
T.L. (1)	1½	613	43	423	147	2·9	N
T.L. (2)	2	760	129	350	281	1·2	N

* See footnote, Table 2.

very likely (hypoglycaemia, hepatomegaly, positive adrenaline test), has so far shown normal lipoprotein patterns at the ages of 18 months and 2 years (see Addendum).

Liver Disease

Congenital Obliteration of Bile Ducts. Two patients were examined (Table 8) and in both the beta fraction was increased and the alpha fraction decreased. In one case (J.M.) the total lipids were also increased; in the other (J.O.) the total lipids, when examined one week after a successful anastomotic operation, were normal.

Neonatal Hepatitis. Three cases were studied (see Table 8); patients A.B. and C.B. were twins. A.B. was only mildly affected and apart from a slightly increased beta/alpha ratio showed no abnormality. His brother was severely affected and ultimately died with cirrhosis at the age of 4 months. During the acute hepatitis stage (C.B.I.) the total lipid and beta fraction were normal but the alpha fraction much reduced. In view of his unsatisfactory progress the effect of cortisone was tried in the hope that it might prevent the onset of cirrhosis; fading of the jaundice and improvement in the patient's general condition ensued. At this stage (C.B.2) the alpha fraction was greater and the beta/alpha ratio less abnormal. Within two weeks of discontinuing cortisone the jaundice deepened and ascites developed. Shortly before death (C.B.3)

TABLE 8

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN PATIENTS WITH LIVER DISEASE

Patient	Age	Diagnosis		Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio	Position of Beta LP Peak, and Character of Beta LP Band*
				Total	Omega	Beta	Alpha	Beta/Alpha	
J.M. ..	10 weeks	Congenital obliteration of bile ducts	Before operation	1,054	74	885	95	9·3	N
J.O. ..	3 months	,,	1 week after successful operation	662	0	622	40	16·0	N
A.B. ..	7 weeks	Neonatal hepatitis	Mild	515	39	366	119	3·1	N
C.B. (1)	7 weeks	,,	Severe	613	48	546	19	30·0	N
(2)	3 months	,,	Improving	588	12	517	59	8·8	N
(3)	4 months	,,	In relapse, shortly before death from cirrhosis	294	0	262	32	8·0	N
S.P. ..	10 months	,,	Shortly before death from biliary cirrhosis	319	0	246	73	3·4	N
C.J. ..	9 years	Infective hepatitis		625	13	569	43	13·0	N
J.P. ..	7 years	,,		637	0	561	76	7·3	N
S.S. ..	10 years	Cirrhosis, probably post-hepatitis	Shortly before death	83	29	52	2	35·3	N
M.H. ..	8 years	Cirrhosis, post-hepatitis		368	88	180	100	1·8	N
M.T. ..	11 years	Congenital hypoplastic anaemia; transfusion haemosiderosis; some evidence of liver damage		1,715	189	1,406	120	12·0	A+

* See footnote, Table 2.

TABLE 9

SERUM LIPID AND LIPOPROTEIN FRACTIONS IN PATIENTS WITH VARIOUS OTHER CONDITIONS

Patient	Diagnosis	Serum Lipid and Lipoprotein (mg. per 100 ml.)				Ratio Beta/Alpha	Position of Beta LP Peak, and Character of Beta LP Band*
		Total	Omega	Beta	Alpha		
D.A.	Essential hyperlipaemia	2,149	2,118	21 ?	10 ?	2·0 ?	Indeterminate
R.H.	Essential hypercholesterolaemia	1,323	53	1,045	225	4·6	N+
J.H.	Essential hypercholesterolaemia	1,980	20	1,584	376	4·1	N+
D.I.	Cretinism	980	69	813	98	8·3	N+
J.B.	Thyrotoxicosis	152	5	117	30	3·9	N
P.F.	Reticulum-cell sarcoma	686	82	501	103	4·5	N
P.H.	Infantile cortical hyperostosis	539	11	458	70	6·5	N
C.M.	Dermatomyositis	515	36	376	104	3·7	N
P.S.	Chronic respiratory infection	588	29	494	65	7·6	N

* See footnote, Table 2.

the total lipid and all fractions decreased markedly.

Another case (S.P.) was also examined shortly before her death from cirrhosis following neonatal hepatitis; there was a similar marked decrease in all lipid fractions.

Infective Hepatitis. Both cases (C.J., J.P., Table 8) were studied during the icteric stage and showed only a much diminished alpha fraction.

Post-Hepatitis Cirrhosis. Cases S.S. and M.H. (Table 8) had exceptionally low lipids due to diminution of the beta and alpha fractions. In both, the omega fraction had an unusual plateau-like shape (Fig. 1D). This pattern was not found in the two cases of cirrhosis following neonatal hepatitis, nor was it seen in any other condition studied.

Congenital Hypoplastic Anaemia (? Liver Damage). M.T. (Table 8), an 11-year-old boy, had received blood transfusions at approximately six-weekly intervals since 3 months of age; haemosiderosis had developed and possibly liver damage. An increased serum globulin concentration (2·1 g. per 100 ml.) strongly suggested such damage, though a normal serum gamma albumin level (4·8 g. per 100 ml.) indicated that advanced cirrhosis was not present.

The total lipid and the beta and omega fractions were grossly increased and the beta band appeared in an advanced position. An interpretation of these findings is difficult, as the pattern does not conform to those found in our other cases of liver disease. The changes seem unlikely to be a reflection of the primary abnormality of erythrocyte formation, as the lipoprotein patterns in two other patients, who were younger and had received fewer transfusions, were normal. Further studies are needed to elucidate the nature of this unexpected abnormality.

Essential Hyperlipaemia

The pattern (Fig. 1E) (in Case D.A., Table 9), which is diagnostic, is characterized by an enormously increased omega fraction, with virtual absence of beta and alpha lipoproteins. The values for the beta and alpha fractions were extremely low and may be inaccurate owing to difficulties in the separation of these fractions in the presence of an overwhelming quantity of chylomicron material.

Essential Hypercholesterolaemia

In these patients (Cases R.H. and J.H., Table 9) the beta fraction was greatly increased. At first sight the pattern (Fig. 1F) appeared similar to that seen in nephrosis but in contrast to the nephrotic pattern the beta lipoprotein was normal in position relative to the globulins. Moreover the alpha fraction was not diminished, and in Case J.H. even elevated.

Cretinism

In Case D.I., aged 15 months, untreated (Table 9), the beta lipoprotein was increased but occupied its normal position. The alpha fraction was diminished, so that the beta/alpha ratio showed a definite elevation. These findings were of special interest, as the serum cholesterol (186 mg. per 100 ml.) was within normal limits.

Thyrotoxicosis

In Case J.B., aged 11 years (Table 9), in contrast to the findings in hypothyroidism, the total lipids were remarkably low and the depletion was noticeable in all the fractions. Serum cholesterol in this patient was 127 mg. per 100 ml., a value likewise within normal limits.

Miscellaneous Conditions

The commonest abnormality found in various conditions comprised a moderate decrease in alpha

lipoprotein, less marked than in nephrosis or jaundice, coexistent with a beta fraction normal in quantity and position. In consequence there was a slight or moderate increase of the beta/alpha ratio.

Cases P.F., P.H., C.M., P.S. (see Table 9) illustrate the diversity of conditions in which this abnormality was found.

DISCUSSION

In some conditions, this technique of lipoprotein electrophoresis yielded diagnostic information; in others, serial patterns, though not diagnostic, were helpful in assessing progress. In our group of cases, the technique was of diagnostic value in nephrosis, idiopathic infantile hypercalcaemia, glycogen storage disease, essential hyperlipaemia, essential hypercholesterolaemia, cretinism, thyrotoxicosis, some forms of liver disease and possibly in Hurler's syndrome.

In the difficult differential diagnosis of congenital obliteration of the bile ducts from neonatal hepatitis this technique might prove helpful. The results suggested that in the early months of life, when correct diagnosis is so important, serum total lipid and beta lipoprotein tend to be higher in obliteration than in hepatitis. In the later stages, as cirrhotic changes complicate both hepatitis and unrelieved obstruction, the total lipid and the beta fraction are likely to become decreased in both conditions and lipoprotein electrophoresis is then unlikely to give diagnostic help.

An unusual plateau shape in the omega fraction profile was observed in association with low total lipids in two older cases of post-hepatitis cirrhosis. This feature was not seen in the infants who developed cirrhosis following obliteration or neonatal hepatitis.

Less specific abnormalities were found in many conditions, e.g., cystine storage disease in the stage of severe glomerular damage, and in various forms of mobilization lipaemia. In such cases repeated examinations were helpful in assessing progress.

In various conditions, notably nephrosis, cystine storage disease, infantile hypercalcaemia, diabetes mellitus and malnutrition with transport lipaemia, the serum beta lipoprotein was found to possess an enhanced electrophoretic mobility. The alpha lipoprotein was seen likewise to vary somewhat in its mobility, and in two cases was advanced so markedly that a part appeared ahead of the serum albumin. Fast-moving beta and alpha fractions have been produced by intravenous injection of heparin (Herbst, Lever, Lyons and Hurley, 1955) and by intravenous laminarin sulphate M (Besterman and Evans, 1957). Presumably a lipolytic process was thereby potentiated, the liberated fatty acids being attached to beta lipoprotein, and in extreme cases to alpha lipoprotein also, with consequent enhancement of their mobility. These findings suggest that in our cases, in response to a nutritional need, mobilization from the lipid stores was occurring with subsequent spontaneous lipolysis.

SUMMARY

A method for separating serum lipoproteins by electrophoresis is described including quantitative evaluation of the fractions and the total lipid.

The normal findings in infants and children are presented, and abnormalities found in various disease states are described. The procedure was of diagnostic value in nephrosis, idiopathic infantile hypercalcaemia, glycogen storage disease, essential hyperlipaemia and hypercholesterolaemia, thyroid disorders and some forms of liver disease. In these and certain other conditions, serial examinations were of value in assessing progress.

In some forms of renal disease and mobilization lipaemia the beta lipoproteins, and sometimes also the alpha lipoproteins, were found in a position ahead of the normal. The significance of this finding is discussed.

We are grateful to Professor J. M. Smellie for his support and interest throughout this work; and thank Dr. H. W. Everley Jones, Dr. J. M. Garvie and members of the consultant staff of the Children's Hospital for access to their patients.

Addendum

Since submitting this paper for publication we have reinvestigated Case T.L. (Table 7), the boy in whom a diagnosis of glycogen storage disease had seemed likely, despite the normal lipoprotein electrophoresis. There is now no hepatomegaly, the adrenalin test is negative, and the diagnosis is ruled out. The high diagnostic value of lipoprotein electrophoresis in glycogen storage disease is thus emphasized.

References

Adlersberg, D., Bossak, E. T., Sher, I. H. and Sobotka, H. (1955) *Clin. Chem.*, **1**, 18.
Besterman, E. M. M. and Evans, J. (1957). *Brit. med. J.*, **1**, 310.
Dangerfield, W. G. and Smith, E. B. (1955). *J. clin. Path.*, **8**, 132.
Fanconi. G. and Girardet, P. (1952). *Helv. paediat. Acta*, **7**, 314.
Gottfried, S. P., Pope, R. H., Friedman, N. H., Akerson, I. B. and Di Mauro, S. (1955). *Clin. Chem.*, **1**, 253.
Grassmann, W., Hannig, K. and Knedel, M. (1951). *Dtsch. med. Wschr.*, **76**, 333.
Herbst, F. S. M., Lever, W. F. and Hurley, N. A. (1955). *J. invest. Derm.*, **24**, 507.
——, ——, Lyons, M. E. and Hurley, N. A. (1955). *J. clin. Invest.*, **34**, 581.
Kunkel, H. G. and Slater, R. J. (1952). *Ibid.*, **31**, 677.
—— and Tiselius, A. (1951). *J. gen. Physiol.*, **35**, 89.
Laurell, C. B. (1955). *Scand. J. clin. Lab. Invest.*, **7**, 257.
Lightwood, R. (1952). *Archives of Disease in Childhood*, **27**, 302.
Rafstedt, S. (1955). *Acta. paediat. (Stockh.)*, **44**, Suppl. 102.
Salt, H. B. (1956). *Clin. Chem.*, **2**, 35.
Schlesinger, B., Butler, N. and Black, J. (1952). *Helv. paediat. Acta*, **7**, 335.
Schwartz, M. and Thomsen, B. (1957). *Brit. med. J.*, **1**, 14.
Studnitz, W. von (1955). *Scand. J. clin. Lab. Invest.*, **7**, 329.
Swahn, B. (1952a). *Ibid.*, **4**, 98.
—— (1952b). *Ibid.*, **4**, 247.
Ulstrom, R. A., Smith, N. J. and Heimlich, E. M. (1956). *A.M.A. J. Dis. Child.*, **92**, 219.

THE URINARY PHENOLSULPHONPHTHALEIN (PHENOL RED) EXCRETION TEST IN HYDROCEPHALUS

BY

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The classification of hydrocephalus into communicating and non-communicating types is still largely based on the dye test introduced by Dandy and Blackfan in 1914 and 1917. They used the appearance of dye in the spinal fluid after its injection into one of the lateral ventricles as the criterion.

In the same papers Dandy and Blackfan described a quantitative urinary dye excretion test. They showed that in cases of hydrocephalus the amount of phenol red which is excreted in the urine in a two-hourly period after its intraventricular or intrathecal injection is less than in cases with a normal cerebrospinal fluid pathway. The excretion patterns fell into two fairly distinct groups according to whether a communication did or did not exist, though it was suggested that there might be an intermediate group with a 'partial' communication. The reduced excretion results were assumed to reflect the reduction of the available absorptive surface in the subarachnoid space. Their observations were based on a small series of cases and in only 15 of their 26 patients was the anatomical site of the blockage causing the hydrocephalus known.

This work was shortly overshadowed by the introduction of pneumoencephalography with its wider application to other conditions (Heuer and Dandy, 1916; Dandy, 1919). The present study was undertaken to explore and develop the possibilities of the urinary dye excretion test in hydrocephalus, and this report is based on 165 dye tests carried out on 101 patients as shown in Table 1. In all these cases the anatomical site of the block has been ascertained, either from satisfactory pneumoencephalography or at post-mortem examination. Tests, which were unsatisfactory because of incomplete urine collection, poor urinary output or some other cause, have been excluded. Few children with a normal cerebrospinal fluid pathway have been tested; those who have been were investigated for suspected hydrocephalus.

TABLE 1

COMPOSITION OF SERIES OF 165 SATISFACTORY TESTS ON 101 VERIFIED CASES

		No. of Tests		No. of Patients
		Intra-ventricular Injection	Intra-thecal Injection	
Physiological	Normal	3	6	8
	Non-communicating ..	48	28	44
	Communicating	53	41	49
Anatomical	S.B.C.	27	20	36
	I.V.B.	20	7	14
	B.C.B.	33	30	37
	I.V.B. and B.C.B. ..	11	12	6
	Total	94	71	101

S.B.C. = spina bifida cystica with hydrocephalus.
I.V.B. = intraventricular block.
B.C.B. = basal cisternal block.

Method

A modification of Dandy and Blackfan's method has been used.

Injection of the Dye. The phenolsulphonphthalein* is supplied in ampoules containing 6 mg. of dye dissolved in 1 ml. of alkali. The whole content of an ampoule is neutralized immediately before use with an equal volume of 0·03% hydrochloric acid supplied. One millilitre (3 mg.) of the neutralized phenol red is then injected into a lateral ventricle or the lumbar theca and the dye is mixed with the cerebrospinal fluid by withdrawing the plunger of the syringe several times. The intraventricular injection is usually carried out three or four days after the intrathecal.

Collection of Urine. All the urine passed during the next 24 hours is then collected in divided specimens

* Messrs. Savory and Moore, Ltd., London, W.1, in boxes of six ampoules of dye and six of acid. Each batch is accurately matched.

at, one, two, four, six, nine, 12, 18 and 24 hours after injections of the dye. As the majority of the subjects are infants, it is advisable to catheterize females and to use Paul's tubing for the males. Care must be taken that no urine is lost, as this may considerably alter the result obtained.

Estimation. It was noticed that the pink dye in the urine faded slightly after 24 hours, especially if kept at room temperature. This is due to some constituent of the urine, for phenol red in water remains unaltered for days or weeks. The urine sample should therefore be stored in a refrigerator, and the dye content estimated within 24 hours of being passed.

The whole of each specimen is rendered alkaline with 10% sodium hydroxide until the intensity of the colour ceases to increase. The volume is then noted. About 10 ml. of the alkaline urine is centrifuged, and the colour intensity of the supernatant fluid is estimated in the photoelectric colorimeter with a No. 604 Ilford filter, using centrifuged alkaline urine as a blank and phenol red as a standard.

The phenol red standard is prepared as follows:

The contents of one ampoule (6 mg. of dye in 1 ml.) are made up to 10 ml. with distilled water to prepare a stock solution, which will keep two weeks or more in a refrigerator. Just before, 0·5 ml. of the stock phenol red solution is then made up to 100 ml. with centrifuged alkaline urine. This will keep for six hours.

Calculation of the Result. The dye content of each specimen (in % of the total injected)

$$= \frac{\text{reading of test} \times \text{volume}}{\text{reading of standard} \times 10}$$

A histogram such as the one shown in Fig. 1 can then be prepared and the total amount of dye excreted in the first six hours calculated.

In order to obtain reliable results, the full cooperation of the ward staff is absolutely essential. All urine losses must be reported accurately; the child must have a good urinary output and anaesthetics must be avoided.

The absorption of dye and the subsequent excretion in the urine should be a smooth process, however slow.

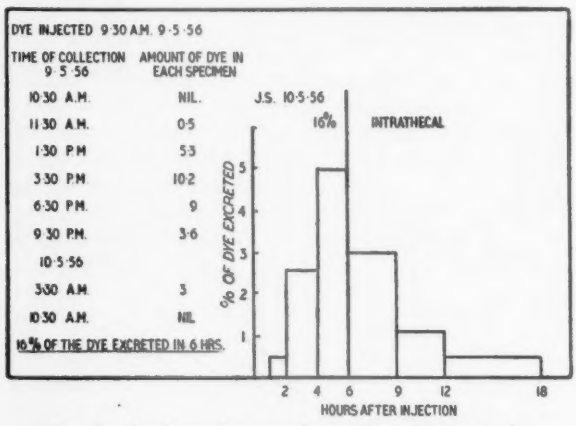

FIG. 1.—Specimen dye excretion results and histogram.

Erratic excretion results indicate that something has gone wrong with the test. This may be due to faulty urine collection or to erratic or suppressed urine production resulting from dehydration, vomiting or recent anaesthesia. To detect some of these errors, urine collection is continued for the whole 24-hour period, rather than the minimum six hours.

Repeated tests on the same patients under similar conditions show that the results are reproducible. When the test is carried out after air studies, the presence of air in the cerebrospinal fluid pathway does not seem to alter the amount of dye excreted. The children tolerate this form of investigation well. A few reactions have occurred, usually in the form of a transient pyrexia. There were, however, two cases of chemical meningitis and one of cortical vein and sinus thrombosis. The severity of these reactions compare favourably with those that follow air studies on hydrocephalic patients, who are known to be easily upset by any form of interference.

Results

To obtain full information with this test both intraventricular and intrathecal dye injection should be carried out. The results are best considered under their various anatomical groups (Fig. 2).

(1) **Normal Cerebrospinal Fluid Pathway.** Only eight children of the series belong to this group. The values obtained after intraventricular are considerably less than those after intrathecal injection. Dye injected into the lateral ventricle, even in a normal ventricular system, is considerably diluted and it then has to flow out into the subarachnoid space before it is absorbed. When the injection is made into the theca, little dilution takes place and absorption begins at once. This accounts for the dye excretion of above 25% after intraventricular, and above 40% after intrathecal, injection in the normal group.

(2) **Basal Cistern Block.** In these cases, the cerebrospinal fluid is able to reach the subarachnoid space, but is prevented by adhesions from going beyond the basal cisterns.

The results obtained after injection into both sites are below normal, but always more than 5%. The ventricular dye result appears to bear little relation to the level of the basal cistern block, but is more an index of the degree of dilatation of the ventricles and the stasis of the cerebrospinal fluid. In the small number of cases in which really accurate ventriculograms are available the amount of dye excreted after intrathecal injection shows a close correlation with the level of the block within the basal cisterns.

(3) **Intraventricular Block.** As in this group the dye injected into the lateral ventricles is prevented

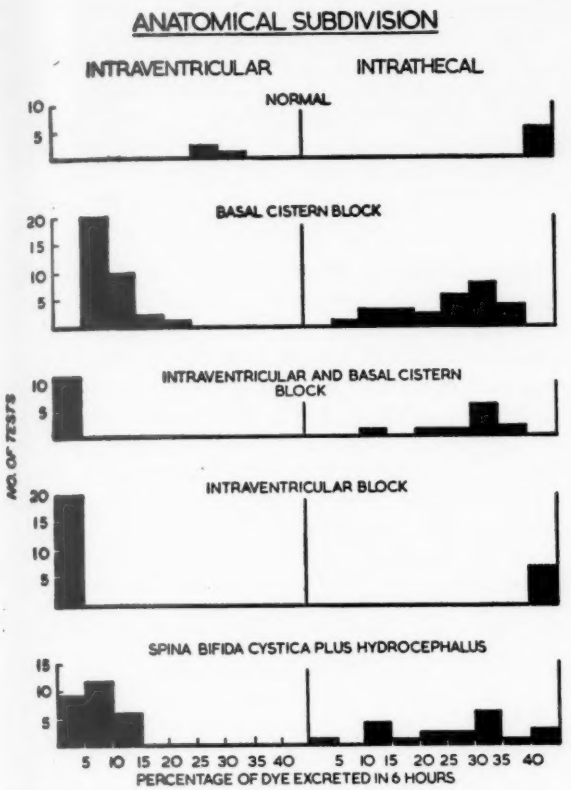
ANATOMICAL SUBDIVISION
INTRAVENTRICULAR
INTRATHECAL
NORMAL
BASAL CISTERN BLOCK
INTRAVENTRICULAR AND BASAL CISTERN BLOCK
INTRAVENTRICULAR BLOCK
SPINA BIFIDA CYSTICA PLUS HYDROCEPHALUS
NO. OF TESTS
5 10 15 20 25 30 35 40 5 10 15 20 25 30 35 40
PERCENTAGE OF DYE EXCRETED IN 6 HOURS

FIG. 2.—Tabulation of the results according to whether a communication did or did not exist. The amount of dye excreted in six hours is plotted horizontally, the number of tests in each 5% dye excretion group vertically. Intraventricular dye excretion results are on the left, intrathecal on the right.

from reaching the subarachnoid space, where it is normally absorbed, it is not possible to distinguish between blocks at any particular level within the ventricular system. Therefore all types of intraventricular block have to be grouped together. Cases with a normal subarachnoid space can, however, be separated from those which have basal cistern block in addition.

INTRAVENTRICULAR BLOCK WITH NORMAL SUBARACHNOID SPACE. Here the block is generally at the level of the aqueduct of Sylvius, and is often a congenital malformation. The excretion figures after injection into the ventricle are always below 5% and often 1% or less, and the dye continues to be excreted in small amounts for a long time. The results after intrathecal injection are similar to those cases with a normal cerebrospinal fluid pathway.

INTRAVENTRICULAR WITH BASAL CISTERN BLOCK. This combined lesion usually results from an infective process. The excretion results after intraventricular injection of dye are indistinguishable from cases which have only an intraventricular block. The values after intrathecal injections, however, are below normal as in cases with a basal cistern block.

(4) **Spina Bifida Cystica and Hydrocephalus.** This group is easily separated from the others on purely clinical grounds. In this condition the hydrocephalus may be due to a malformation at the level of the aqueduct or at the foramen magnum (Arnold-Chiari malformation). Ascending infection from the spinal malformation may give rise to a spinal block, occlusion of the exit foramina of the fourth ventricle aqueduct block or a basal cistern block. As any combination of these lesions may be present in a particular case, a wide range of excretion results is obtained.

Discussion

The results are comparable with those of Dandy and Blackfan, and confirm some of their findings. Throughout their investigation these authors, however, obtained higher excretion values which produced less definite results.

In Fig. 3, when the findings of this investigation are tabulated according to the presence or absence of communication, there is considerable overlapping in the results of the two groups, as in Dandy and Blackfan's series, and no reliable conclusions can be

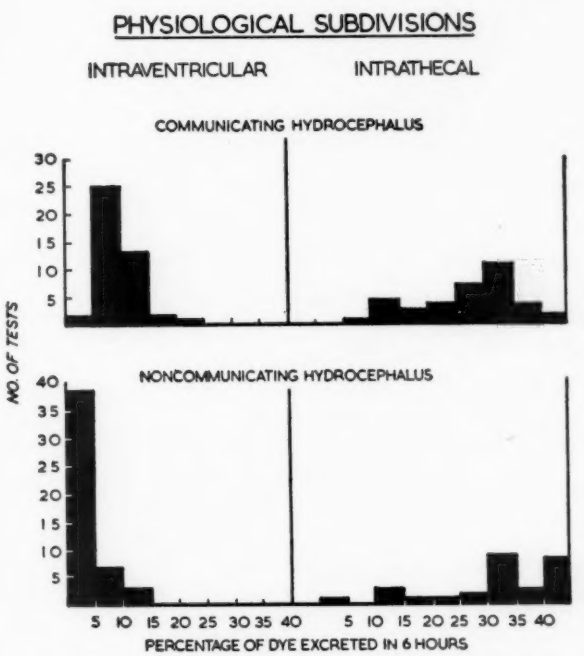
PHYSIOLOGICAL SUBDIVISIONS
INTRAVENTRICULAR
INTRATHECAL
COMMUNICATING HYDROCEPHALUS
NONCOMMUNICATING HYDROCEPHALUS
NO. OF TESTS
5 10 15 20 25 30 35 40 5 10 15 20 25 30 35 40
PERCENTAGE OF DYE EXCRETED IN 6 HOURS

FIG. 3.—Tabulation of the results according to the anatomical site of the block. The amount of dye excreted in six hours is plotted horizontally, the number of tests in each 5% dye excretion group vertically. The intraventricular dye excretion results are on the left, intrathecal on the right.

drawn. To account for this, Dandy and Blackfan suggested that cases with a 'partial' communication must exist.

If the results are tabulated according to the anatomical site of the block, however, clear-cut groups with distinct dye excretion patterns emerge. Conversely from the dye excretion patterns, the anatomical site of the block can be deduced. In the groups associated with spina bifida cystica, very variable excretion results are obtained for reasons which have already been given. Even here information, often difficult to obtain by other methods, can be deduced regarding the position of the obstructions and the state of the subarachnoid space. In the cases with combined ventricular and basal cisternal block, where the ventriculogram will demonstrate the site of the intraventricular block only, dye studies will give information about the basal cisterns as well. Thus there is no need for a difficult lumbar encephalogram. This is important when a ventriculocisternostomy is to be performed, an operation which could not succeed when the basal cisterns are impermeable.

Guthkelch (1955) claimed that dye tests in hydrocephalus were misleading. This may be true of the simple dye test for communication, but not of the phenol red dye excretion test when it is carefully performed. This test is not intended to replace good air encephalography but is likely to prove a really useful ancillary investigation, and of value when the *x*-ray pictures are not entirely reliable, or when adequate facilities are not available.

The test has been found useful in assessing the results of operation by comparing excretion values before and after. An adaptation of the method is being used with considerable success to select patients for a new form of ventriculo-subdural drainage (Forrest, Laurence and Macnab, 1957). It is hoped that eventually high excretion rates will be of value in predicting whether a case is likely to arrest naturally or not.

Summary

The method of the urine phenolsulphonphthalein excretion test as used in hydrocephalic children is described. Distinct dye excretion patterns were obtained in 101 patients, corresponding to the anatomical site of the blocks. The test was found of value as an ancillary to good pneumoencephalography; it could replace poor radiographs and gave additional information when there is a combined ventricular and basal cisternal block. The test may prove to be of prognostic value.

Dr. A. L. Woolf carried out the preliminary tests. I wish to thank the staff of The Hospital for Sick Children and of the Westminster Children's Hospital, and especially Mr. G. H. Macnab and Dr. M. Bodian, for their cooperation and advice; Miss M. Shorts and Miss B. Glashier for their technical assistance, Mr. G. Lyth for the charts, and the Research Committee of The Hospital for Sick Children for its financial support.

References

Dandy, W. E. (1919). *Ann. Surg.*, **70**, 397.
—— and Blackfan, K. D. (1914). *Amer. J. Dis. Child.*, **8**, 406.
——, —— (1917). *Ibid.*, **14**, 424.
Forrest, D. M., Laurence, K. M. and Macnab, H. G. (1957). *Lancet*, **1**, 1294.
Guthkelch, A. N. (1955). *Proc. roy. Soc. Med.*, **48**, 849.
Heuer, G. J. and Dandy, W. E. (1916). *Bull. Johns Hopk. Hosp.*, **27**, 311.

REDUCING SUGARS IN THE URINE AND BLOOD OF PREMATURE BABIES

BY

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We reported previously the finding by paper chromatography of reducing sugars in the urines of 24 out of 50 normal full-term babies (Haworth and McCredie, 1956). We suggested that the galactose which we found in the urines of 13 of the 50 babies might be related to the functional inefficiency of the liver that is so commonly a feature of the newborn. If this were so it might be expected that premature babies, in whom the liver is less efficient functionally than in full-term babies, and in whom 'physiological' jaundice is therefore more frequent and more marked, would excrete reducing sugars to a greater degree than babies born at full term. We therefore examined the urines of 26 male premature babies by paper chromatography and the blood of 10 of them after feeds. This paper is the report of our findings.

Method

Urines were examined from an unselected group of 26 male premature babies. Twenty-two of them were born at the Jessop Hospital for Women, Sheffield, two were born at home and admitted to the same hospital on the first day of life and two others were born at home and admitted to the Children's Hospital, Sheffield, on the second and third days of life respectively.

The birth weights of the babies varied from 2 lb. 15 oz. to 5 lb. 5 oz. and their estimated gestation varied from 32 to 40 weeks.

It was planned to collect urines from each baby on the first day of life and thereafter on alternate days until the baby was discharged from hospital, that is, when its weight approached 5½ lb. This did not prove possible in every case, although in most cases the first urine was examined before the baby had received a feed. In three cases urine collection had to be abandoned or interrupted because of skin irritation or soreness caused by the adhesive strapping used to hold the collecting tubes in position.

All babies were fed with breast milk. In the case of the smaller babies the feeding was not started until the second or third day of life and most were given a few feeds of glucose water before the breast milk was offered. In most cases it was not possible to correlate the times of feeding with the times of micturition.

The degree of clinical jaundice of the first 14 babies was recorded each day by the same observer under similar conditions of light and serum bilirubin was estimated only if deep jaundice was present. In Cases 15-26, however, routine estimations of the serum bilirubin were made, usually on the third, fifth and seventh days of life.

The chromatographic technique employed for the urines was similar to that described in our previous report, except that the triangular-shaped filter papers were bisected after removal from the solvent. By this means different developers could be sprayed on to the two halves if required as described by Horrocks and Manning (1949).

Blood was obtained from heel pricks, about ½ ml. being taken into small dry tubes. Enough 20% trichloracetic acid was then added to precipitate all the protein (usually about five drops) and after centrifuging 50 µl. of the supernatant fluid was applied direct to the filter paper. The procedure then was identical with that employed for the urines.

Results

Urines. One hundred and fifty-two urines from 26 babies were examined and the results are shown in Tables 1 and 2.

TABLE 1

NUMBER OF PREMATURE BABIES AND URINES IN WHICH REDUCING SUGARS WERE FOUND

Reducing Sugar	No of Babies Excreting Sugar on One or More Occasions	No of Urines Containing Sugars
Glucose	10	22
Galactose	17	62
Lactose	17	37
Xylose	6	8

Twenty babies excreted glucose, galactose, lactose or xylose, or combinations of these sugars, on one or more occasions.

Four babies did not excrete any sugar on any occasion; two babies excreted only an unidentified reducing substance.

Seventy-seven, or 51%, of the 152 urines examined contained one or more reducing sugars.

Three of the babies died with atelectasis when they were 1, 3 and 4 days old respectively. Urine from

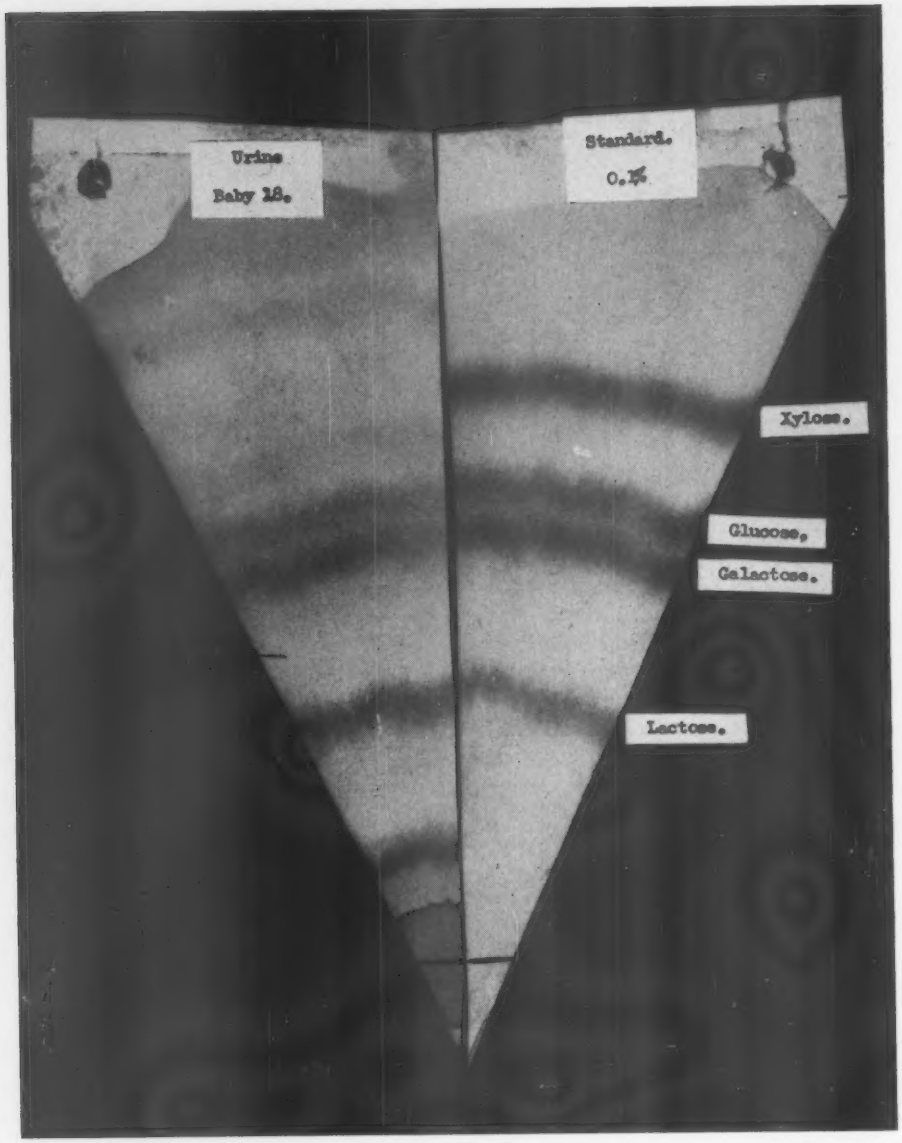

FIG. 1.

TABLE 2
AGES OF 26 PREMATURE BABIES WHEN URINES EXAMINED

	Age in Days of Babies Examined											Totals*
	1	2	3	4	5	6	7	8–14	15–21	22–28	<28	
No. of urines containing glucose		2	5		2	1	3		6	2	1	22
No. of urines containing galactose		1	2	3	6	6	7	14	10	5	9	62
No. of urines containing lactose		2	2	7	5	3	5	5	4	2	2	37
No. of urines containing xylose		3	3	1	1							8
Total no. of urines containing reducing sugars		5	8	7	7	5	7	14	10	5	9	77
Total no. of urines containing no reducing sugars	7	7	5	3	5	3	5	20	8	7	5	75
Total no. of urines examined	7	12	13	10	12	8	12	34	18	12	14	152

* Many of the urines contained more than one sugar and therefore the totals of urines containing each sugar do not represent the total number of urines examined

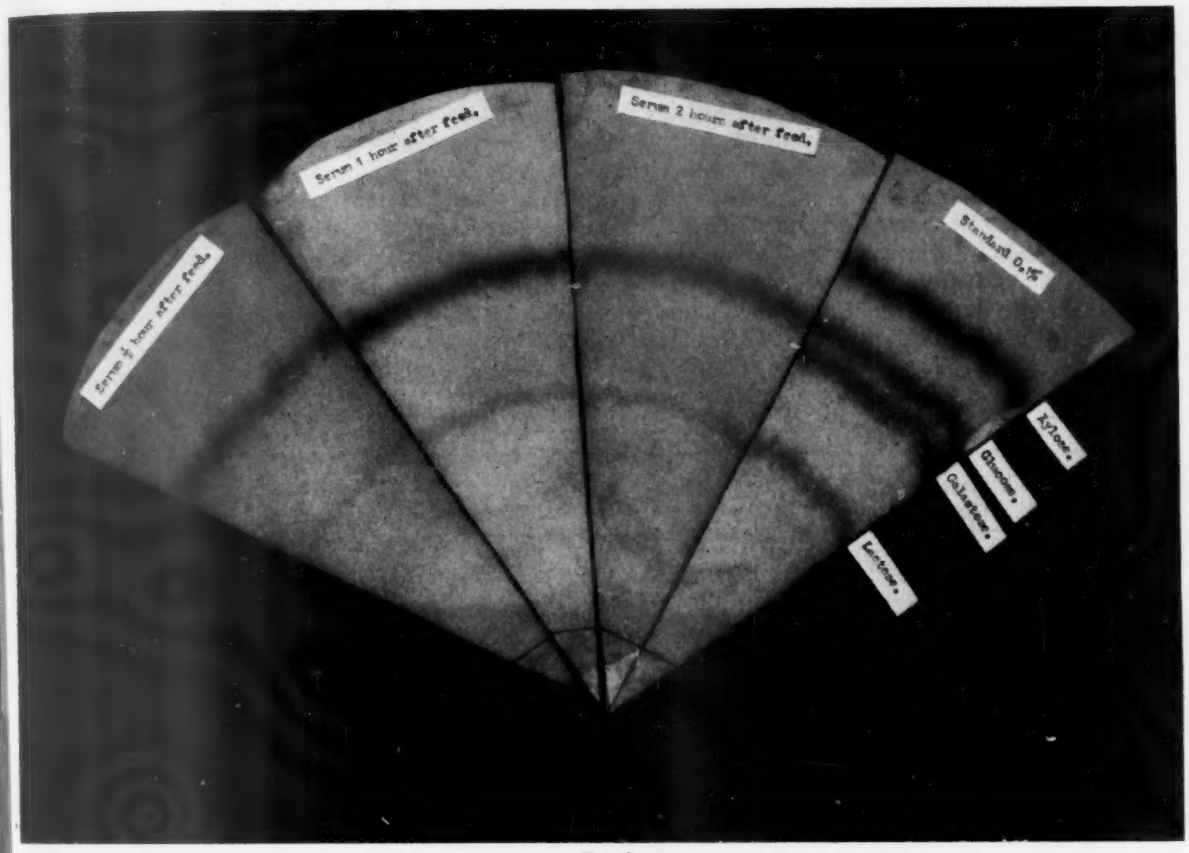

FIG. 2.

one of these babies was collected before the first feed and it did not contain any reducing sugar; urine from another, collected after it had received one breast feed, contained glucose and xylose. From the third, two specimens were collected, the first of them, passed before a feed, contained xylose and the other, passed after a feed, contained lactose.

Four of the babies developed hyperbilirubinaemia (not due to blood incompatibility) and exchange transfusions were performed when the serum bilirubin figures reached 20 mg./100 ml. One baby had two exchange transfusions. Of these four babies, one excreted sugars in two out of three urines collected, another in 12 out of 16, the third in six out of 11 and the fourth in one out of two. These babies eventually made complete recoveries.

One baby developed minor umbilical sepsis and another showed signs of cerebral irritability, but these also eventually made good progress. The remaining 17 babies were healthy.

Urines were collected from 15 of the babies before they had received a feed. Of these urines, 11 contained no reducing substance, two contained an unidentified reducing substance, one contained xylose and another glucose.

Most of the babies excreted less than 100 mg./100 ml. of sugar but it was estimated that one baby excreted between 100 and 200 mg./100 ml. of galactose on the 30th day of life and four babies excreted the same amount of lactose on one occasion each. Fig. 1 shows the chromatogram of the urine collected from Case 18 on the fifth day of life. Lactose in a concentration of more than 100 mg./100 ml. is shown together with glucose and galactose in smaller amounts. No correlation was found between the number and type of sugars excreted and the degree of jaundice or the serum bilirubin levels of the babies. Neither was there any correlation between the sugars excreted and the degree of prematurity as assessed by birth weight or length of gestation.

Blood. From 10 babies specimens of capillary blood taken after milk feeds were chromotographed and the results are shown in Table 3. It will be seen that in two instances sugars other than glucose

were found. Galactose was found with glucose on the 15th day of life in Case 15, but unfortunately it is not recorded how long after a feed this specimen was passed. Lactose was found with glucose half, one and two hours after a feed on the 13th day of life in Case 20 (Fig. 2). From babies 20, 21 and 23, urines were collected while blood samples were being taken and the results are shown in the last column of Table 3. A and B were two female babies from whom urines were not collected. No reducing sugar was found in blood taken two hours after a feed in Case 23, but this may have been because the specimen was too much diluted by an excess of trichloracetic acid.

Discussion

As shown above, 20 of 26 premature babies excreted reducing sugars in the urine, on one or more occasion, during the first few days or weeks of life. Of 152 urines examined from the 26 babies, 77 (51%) contained one or more sugars. Galactose and lactose were the sugars most commonly found and their source was almost certainly the gut. Neither of these sugars was found in the urine of any baby before a milk feed had been given.

Although there was no correlation between the birth weights of the babies and the sugars excreted, the numbers in the lower birth weight ranges were small and if a larger group had been examined some

TABLE 3
RESULTS OF BLOOD CHROMATOGRAPHY

Case	Birth Weight (lb. oz.)	Age in Days	Time after Feed	Feed	Approximate Lactose Content (g.)	Reducing Sugars	Urines passed in Relation to Feeds
15	3 10	15	Unspecified	1½ oz. breast milk	3·3	Glucose and galactose	
		20	,,	1½ oz. breast milk	3·3	Glucose	
16	5 10	4	1 hour	2 oz. ½ cream Nat. dried milk 3 oz. ½ cream Nat. dried milk	Formula of feed not recorded	Glucose	
		9	1 hour			Glucose	
17	5 2	9	1 hour	Breast fed and not test weighed	Not known	Glucose	
18	5 3	4	1 hour	½ oz. half-strength breast milk	0·6	Glucose	
		9	1 hour	1 oz. breast milk	2·2	Glucose	
19	4 13	10	1 hr. 10 min.	1 oz. breast milk	2·2	Glucose	
		12	half-hour	1½ oz. breast milk	3·3	Glucose	
			1 hour			Glucose	
			2 hours			Glucose	
20	4 8	6	1 hour	3 dr. breast milk	0·9	Glucose	
		13	half-hour	1½ oz. breast milk	2·75	Glucose and lactose	
			1 hour			Glucose and lactose	
			2 hours			Glucose and lactose	
		20	Before			Glucose	
			half-hour	1 oz. breast milk	2·2	Glucose	1–2 hours after feed—glucose
			1 hour			Glucose	
			2 hours			Glucose	
21	4 12	3	half-hour	1 oz. breast milk	2·2	Glucose	2 hours after feed—galactose
			1 hour			Glucose	
			2 hours			Glucose	
		8	Before	1½ oz. breast milk	3·3	Glucose	1–2 hours after feed galactose and lactose
			half-hour			Glucose	
			1 hour			Glucose	
			2 hours			Glucose	
23	5 3	6	Before	1½ oz. breast milk	2·75	Glucose	¾ hour after feed galactose and lactose
			half-hour			Glucose	
			1 hour			Glucose	
			2 hours			Nil	
A	3 12	7	Before	2 dr. breast milk	0·6	Glucose	
			half-hour			Glucose	
			1 hour			Glucose	
			2 hours			Glucose	
B	5 5	2	Before	1 oz. breast milk	2·2	Glucose	
			half-hour			Glucose	
			1 hour			Glucose	
			2 hours			Glucose	

correlation might have been found. The figures for sugar excretion in the whole group of premature babies, however, may be compared with those of a group of 50 full-term babies, of whom 24 (48%) excreted sugars in 25 (31%) of 81 urines examined (Haworth and McCredie, 1956). The higher proportion of sugars excreted by the premature babies is statistically significant and it would therefore seem that they are unable to metabolize galactose and lactose as well as full-term babies.

If galactose is excreted in the urine because a functionally inefficient liver is unable to metabolize it fully after absorption, it might be expected that those babies who became more jaundiced would excrete galactose more often than babies who did not show jaundice. In fact no such association between jaundice and galactose excretion was found, and even the four babies whose serum bilirubin levels rose to more than 20 mg./100 ml., and were therefore given exchange transfusions, did not excrete galactose to a higher degree than several babies who never became jaundiced or whose highest bilirubin level was below 5 mg./100 ml. The giving of exchange transfusions may, however, have influenced the excretion of sugars, but we have no information about this. As Table 2 shows, galactose was often found in urines of babies who were over 28 days old when jaundice had long since faded and when liver function had presumably become normal. This may be compared with the observation that in the group of full-term babies, already referred to, galactose was excreted on the sixth and seventh days of life less often than on the third, fourth and fifth.

Another possible cause for the galactosuria is that the ductus venosus may remain patent for a time after birth, thus allowing some portal blood carrying galactose to bye-pass the liver and to empty directly into the systemic circulation. van Creveld (1929) thought that this might be a possible cause for the hypoglycaemia found in premature babies in the neonatal period, although he thought functional immaturity of the liver was a more likely cause. It is known that the ductus venosus may remain patent anatomically for as long as two months after birth (Scammon, 1923), but there is no evidence that it remains functionally patent after birth. Lind's (1953) observations in full-term babies suggest that it does not.

The lactosuria found in 17 of the babies (37 urines) and the lactose found in the blood of Case 20 after a milk feed indicate that not all the lactose is hydrolysed in the gut but that a proportion of it is absorbed unsplit and is excreted because it cannot be metabolized. It can only be assumed that this is due to inadequacy of lactase. Lactose was found in urines of babies as old as 4 weeks, but the figures in Table 2, although small, do suggest that a higher proportion of urines containing lactase was collected from babies aged 4-7 days. This might indicate an increasing ability of the older babies to hydrolyse lactose. Ibrahim (1910) stated that lactase is the last of the disaccharide-splitting enzymes to appear and is often absent until the eighth foetal month.

It might be considered surprising that galactose and lactose were not found more often in the blood samples taken after feeds, especially when these sugars were found in the urines (Cases 21 and 23) passed during the collection of the blood. It is possible that the concentration of the sugars in the blood was too low on many occasions to be demonstrated by the method used.

Xylose was found in eight urines from six babies, on one occasion before a feed had been given. This feature was not found after the fifth day of life and its source remains obscure.

Summary

Urines from 26 male premature babies were examined for reducing sugars by paper chromatography. Twenty babies excreted glucose, galactose, lactose and xylose or combinations of these sugars on one or more occasions. Reducing sugars were found in 77 of 152 urines examined.

Sugars were found more frequently in the urines of these premature babies than in a group of full-term babies.

Blood from 10 premature babies was examined for reducing sugars after milk feeds. In one, galactose was demonstrated and in another, lactose.

Thus premature babies are not able to metabolize galactose and lactose fully and the possible causes of this are discussed.

We are grateful to Dr. T. Colver and Professor R. S. Illingworth for permission to investigate the premature babies under their care and to them and Dr. J. L. Emery for helpful criticism. We also thank Miss E. Finch for giving us laboratory facilities and the sisters at the Jessop Hospital for Women for their help in collecting the urines.

References

Creveld, S. van (1929). *Amer. J. Dis. Child.*, **38**, 912.
Haworth, J. C. and McCredie, D. (1956). *Archives of Disease in Childhood*, **31**, 189.
Horrocks, R. H. and Manning, G. B. (1949). *Lancet*, **1**, 1042.
Ibrahim, J. (1910). *Hoppe-Seyl. physiol. Chem.*, **66**, 19.
Lind, J. (1953). In *Anoxia of the New-born Infant: A Symposium organized by the Council for International Organizations of Medical Sciences*, p. 184. Oxford.
Scammon, R. E. (1923). In *Pediatrics*, edited by Abt, I. A. Vol. 1, p. 388. Philadelphia and London.

CONGENITAL IDIOPATHIC HYPOGAMMAGLOBULINAEMIA

BY

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Since Bruton (1952) first described the syndrome of congenital agammaglobulinaemia associated with decreased resistance to infection in an 8-year-old boy, further cases in boys have been reported. Good and Mazzitello (1956) found 18 cases of congenital agammaglobulinaemia in the literature and described a further six cases in boys. Familial agammaglobulinaemia affecting male siblings has been described by Kulneff, Pedersen and Waldenström (1955) and by Elphinstone, Wickes and Anderson (1956). We have traced over 30 cases of congenital hypogammaglobulinaemia reported in boys but have only been able to find a few references to the syndrome in girls. Delaitre and Fonty (1955) reported congenital agammaglobulinaemia associated with recurrent infections in a 13-month-old girl, Arnaud-Battandier, Cabannes, Legendre and Sarfaty (1955) described the condition in a 16-month-old girl who died shortly after diagnosis, and Good and Zak (1956) mention a girl who appeared to be suffering from congenital agammaglobulinaemia but give no details.

Deficiency of serum gamma globulin has been reported in girls without any increased susceptibility to infection and Schick and Greenbaum (1945) reported this in an 11-year-old girl with oedema from birth.

There is at the time of writing one other female case of congenital hypogammaglobulinaemia included in the Medical Research Council's treatment trial for hypogammaglobulinaemia. This is a 3-year-old girl, but, unlike the case we report, she has no leucopenia or hepatosplenomegaly (Rubie, 1956).

Case History

M.S., now aged 3 years 8 months, was delivered normally at term on March 18, 1953. Her birth weight was 8 lb. 4 oz. and her neonatal period uneventful. She remained healthy until the age of 8 months.

She is the first child of unrelated, healthy parents. She has a sister aged 22 months who has always been healthy and a step-sister aged 6 years who had recurrent tonsillitis before tonsillectomy.

She was vaccinated against smallpox at the age of 4 months and gave a typical primary vaccinia response without complication. Diphtheria and pertussis immunization was completed at the age of 8 months.

From infancy she had had a history of constant infection.

November, 1953. Left otitis media. Spleen found to be enlarged.

December, 1953. Bronchitis and mild enteritis treated at home.

January, 1954. First admission to hospital. Recurrence of left otitis media and bronchopneumonia, signs mainly at the left base. Unsatisfactory response to penicillin, responded to aureomycin but relapsed and was finally controlled by streptomycin. Spleen and liver both palpable one fingerbreadth below the costal margins. Also normocytic, hypochromic anaemia, haemoglobin 60%, no reticulocytosis. Bone marrow normal. No response to oral iron therapy. Haemoglobin, following 250 ml. of whole blood, rose to 90%.

February, 1954, to February, 1955. Repeated upper respiratory infections and recurrent otitis media; two attacks of stomatitis; chickenpox and an illness diagnosed as measles.

March, 1955. A further attack of stomatitis, responded to local treatment. Haemoglobin 64%, microcytic, hypochromic anaemia. No response to oral iron therapy.

April, 1955. Measles with recurrence of left otitis media. Second admission to hospital with chronic left otitis, purulent rhinitis, marked loss of weight, spleen palpable one fingerbreadth below costal margin. Haemoglobin 50%. Infections responded to local treatment. Discharged home on oral iron therapy.

May, 1955. Third admission to hospital. Recurrence of purulent rhinitis with severe epistaxis, pyodermia of legs, liver palpable one fingerbreadth and spleen two fingerbreadths below costal margins. Bilateral palpable cervical lymph nodes. Haemoglobin 26%, platelets normal. Infections failed to respond to penicillin, but responded to terramycin. Anaemia corrected by blood transfusion, and, following this, general condition improved. Bone marrow biopsy showed a hypoplastic reaction. On June 11, 1955, purulent rhinitis recurred,

together with bilateral otitis media. These infections responded to penicillin. A two weeks' course of formyl tetrahydropteroylglutamic acid ('leucovorin') failed to improve the relative neutropenia. Haemoglobin was 88% on discharge.

June, 1955. Ulcerative stomatitis, responded to local treatment at home. Spleen enlarged.

August, 1955, to November, 1955. Recurrent chronic left otitis media, recurrent rhinitis and bronchitis. Liver and spleen remained palpable two fingerbreadths below costal margins. Haemoglobin varied between 66% and 76%.

December, 1955. Fourth admission to hospital. Exacerbation of left otitis media, and bronchopneumonia with right middle lobe consolidation. Liver and spleen enlarged as previously. Infections responded to terramycin. On January 3, 1956, she developed acute haemolytic streptococcal tonsillitis which responded to penicillin. Haemoglobin on discharge 84%.

January, 1956. Gastro-enteritis, responded to treatment at home.

February, 1956, to April, 1956. Further upper respiratory infections, otitis media and bronchitis.

April, 1956. Fifth admission to hospital. Bronchopneumonia with consolidation at left base, chronic left otitis media and purulent vaginitis. Liver and spleen still enlarged. Palpable cervical lymph nodes. Infections responded to terramycin. Serum proteins were estimated and hypogammaglobulinaemia confirmed by paper electrophoresis. On April 22 recurrence of pneumonia which responded to penicillin. Haemoglobin 64%. On June 5 exacerbation of left otitis media and rhinitis which responded to local treatment.

At this time the diagnosis was confirmed and treatment with intramuscular injections of gamma globulin was begun.

Pathological Investigations. The results of some of the haematological investigations related to her state of health during the period March, 1955, to November, 1956, are summarized in the table.

PLASMA PROTEINS. April 12, 1956. Total serum protein 6·0 g. per 100 ml. (albumin 4·8, globulin 1·2, A:G ratio 4:1). Almost no turbidity was produced with zinc sulphate and paper electrophoresis showed no detectable gamma globulin (Fig. 1a). Examination by a photoelectric densitometer revealed a very small amount of gamma globulin (Fig. 1b). Dr. P. G. H. Gell failed to demonstrate the presence of gamma globulin by his immunochemical technique.

The levels of gamma globulin obtained on further serum by other methods of analysis varied but were all below 100 mg. per 100 ml.

May 2, 1956. Total serum protein 6·16 g. per 100 ml. Electrophoretic analysis: albumin 62·1%, alpha globulins 16·4 %, beta globulins 20%, gamma globulin 1·6% (98·6 mg. per 100 ml.). Estimation of gamma globulin by red blood cell agglutination technique gave a result of approximately 5 mg. per 100 ml.

Classical electrophoretic analysis carried out 13 weeks after treatment with gamma globulin was begun

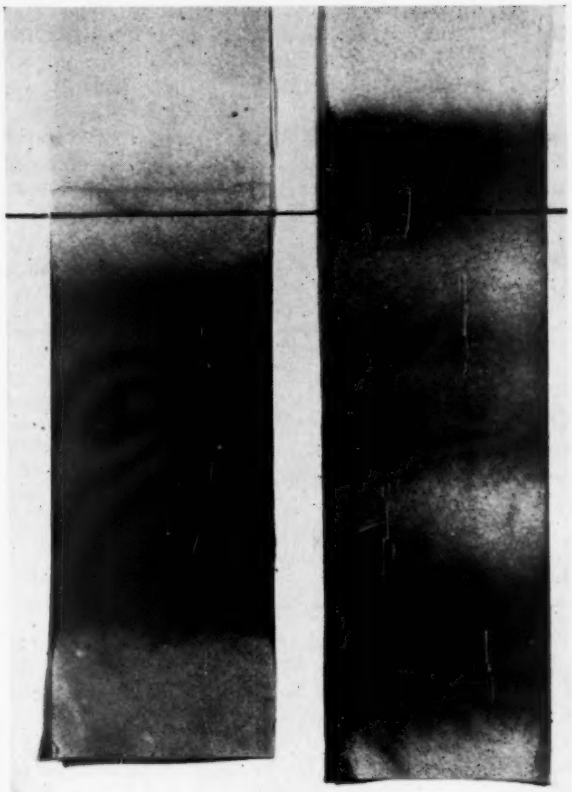

FIG. 1(a).—Paper electrophoresis (May, 1956) before beginning of treatment with gamma globulin.

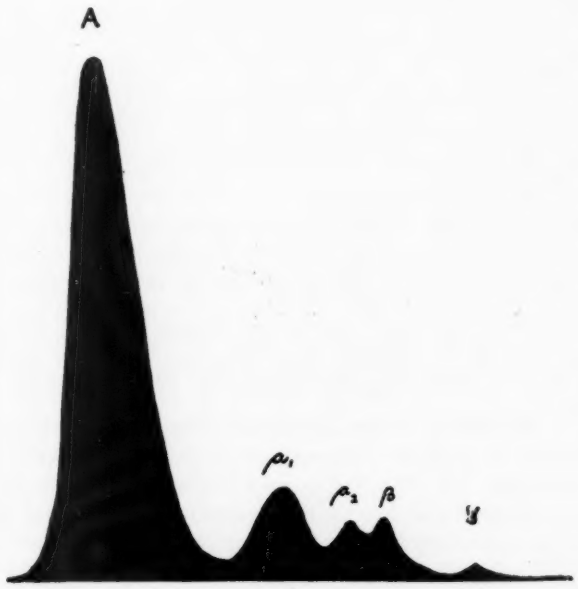

FIG. 1(b).—Graph obtained from 1(a) by examination with a photoelectric densitometer.

gave the following results: albumin 69·2%, alpha globulin 7·5%, beta globulin 13·9%, gamma globulin 1·75%. These figures represent the mean of the ascending and descending electrophoretic patterns (Fig. 2).

Paper electrophoresis after four, 12 and 24 weeks' treatment showed no appreciable change in the serum gamma globulin levels. Fig. 3 shows the pattern obtained on November 5, 1956, 24 weeks after the start of treatment. Estimations of serum proteins and electrophoresis of the patient's parents and sister were normal.

SERUM ANTIBODY LEVELS. The following results were obtained from tests on May 22, 1956.

Serum	Antibody
Antistreptolysin	Less than 50 units/ml.
Antistaphylolysin	None detectable.
Poliomyelitis	No neutralizing antibodies to any of three types in serum dilution of 1:4 against 100 tissue culture doses of virus.
Herpes simplex	None in undiluted serum.
Vaccinia	Negative at 1/2 dilution (neutralization test).
Vaccinia	Negative at 1/2 dilution (haemagglutination inhibition test).
Diphtheria	Less than 1/1,000 unit per ml.
Influenza A and B	Negative.
Mumps	Negative (haemagglutination inhibition test).

Biopsy of Cervical Lymph Node. A biopsy of a cervical lymph node on August 20, 1956, showed distortion of the normal follicular pattern and absence of plasma cells. In addition some areas of the sections showed granulomatous lesions without necrosis, the appearance of which was very suggestive of a tuberculous or sarcoid lesion. Search of Ziehl Neelsen-stained sections failed to reveal any evidence of tubercle bacilli.

Other Investigations. Culture of repeated nose and throat swabs failed to show that any particular organism was responsible for the infections.

On January 25, 1954, bone marrow biopsy showed a normal picture but on May 26, 1955, a hypoplastic reaction.

The blood group was A Rhesus positive. No anti-B isohaemagglutinins detectable. Liver function tests in April, 1956, including bromsulphthalein excretion tests, were normal.

Urine was normal.

The Schick test was positive on May 10, 1956.

Mantoux tests (1 in 1,000 on January 31, 1954, April 20 and December 15, 1955, 1 in 10 on October 29, 1956) were negative.

The clinical diagnosis of pneumonia was confirmed radiologically on three occasions. A radiograph of the chest 12 weeks after the start of treatment was normal.

Treatment. Treatment with intramuscular injections of pooled human gamma globulin was begun on May 23, 1956, the dosage given being in accordance with the Medical Research Council's trial in the treatment of hypogammaglobulinaemia.

In the first week she received 0·95 g. per kg. body weight on three occasions and thereafter this dosage was given once weekly for a period of four months. In accordance with the trial the dosage was reduced to 0·025 g. per kg. body weight per week. She has now been receiving weekly injections of gamma globulin for a period of six months.

Progress. She has shown a satisfactory response to treatment and has had no major respiratory infections since the gamma globulin was begun in May, 1956. During the first nine weeks of treatment she remained very well, suffered no infections and gained 6 lb. in weight. Most striking of all was the change in her general health and behaviour. From being a child who previously had shown little interest in her surroundings or other children, she became an active, contented child who enjoyed playing with her friends. She had acute coryza at the beginning of August, 1956, but this infection resolved spontaneously without complications.

ANTERIOR POLIOMYELITIS. On August 27, 1956, 14 weeks after the beginning of treatment with gamma globulin, she became anorexic and irritable, although when seen on this date she was apyrexial and had no localizing signs of infection. Four days later she was seen again because of weakness of the lower limbs and she was admitted to hospital with anterior poliomyelitis.

The symptoms before the onset of the paralysis were mild and when admitted her temperature was 98·2° F. and there was no complaint of headache, no neck stiffness and Kernig's sign was negative. She had some weakness of both lower limbs and the right knee jerk was diminished. The cerebrospinal fluid findings were as follows: leucocytes 160 per c.mm. (polymorphs 75%, lymphocytes 25%) protein 70 mg. %, chlorides 700 mg. %, sugar 57 mg. %. She had a moderately severe paralytic illness with almost complete paralysis of both legs and a partial paralysis of the left arm. The paralysis was maximal on September 6, 1956, 12 days after the onset of the pre-paralytic symptoms. She was in the isolation hospital for five weeks and while there developed acute tonsillitis which responded to treatment with penicillin.

She returned to our care for physiotherapy on October 8, 1956, and shortly afterwards had a further attack of tonsillitis. This appeared to respond to terramycin, but a few days after treatment was discontinued the infection relapsed, necessitating the use of penicillin and streptomycin. Since November 1 she has had no further infections, although her temperature has never remained consistently normal. Twelve weeks after the onset of poliomyelitis she still has considerable residual muscle weakness of both lower limbs although recovery of function is continuing in response to

physiotherapy. The paralysis of the left arm has almost completely recovered.

The enlargement of the liver and spleen began to recede from the time treatment was begun, and by August 1, 1956, the spleen was only just palpable below the costal margin. Since October 8 it has been impalpable. The liver still remains palpable but only one fingerbreadth below the costal margin. Since the fourth week of treatment the haemoglobin has shown a rise and varied between 76% and 84%, and the total white cell count has on average been higher than before the administration of gamma globulin. There was still no significant leucocytosis at the time of the child's most recent infection.

Discussion

Agammaglobulinaemia is a metabolic disorder characterized by an increased susceptibility to bacterial infections, deficiency of gamma globulin in the serum, deficient antibody formation and failure of immunological response to antigenic stimulation. This syndrome is distinct from hypogammaglobulinaemia or agammaglobulinaemia occurring in other diseases such as the nephrotic syndrome, malnutrition and the syndrome of hypoproteinaemia and oedema associated with atrophic changes in the liver described by Thompson, McQuarrie and Bell (1936).

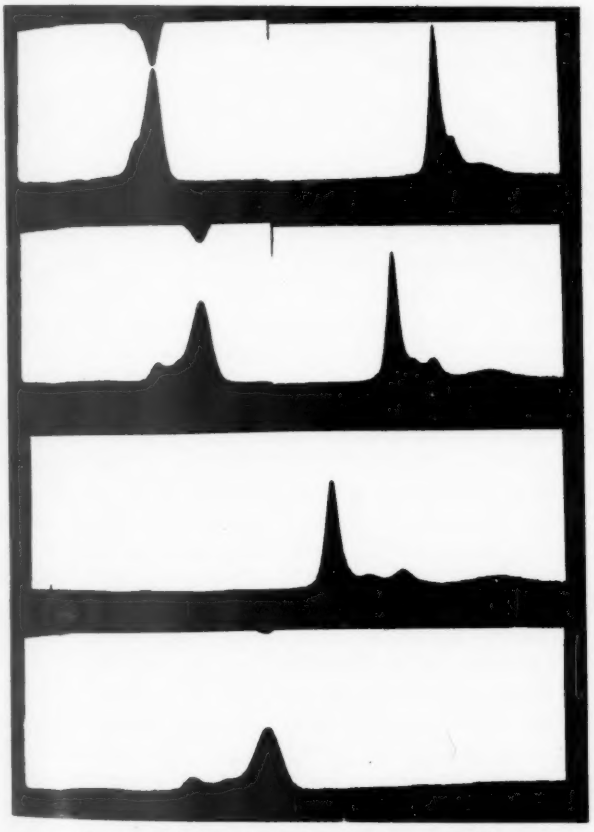

FIG. 2.—Classical electrophoresis (August, 1956).

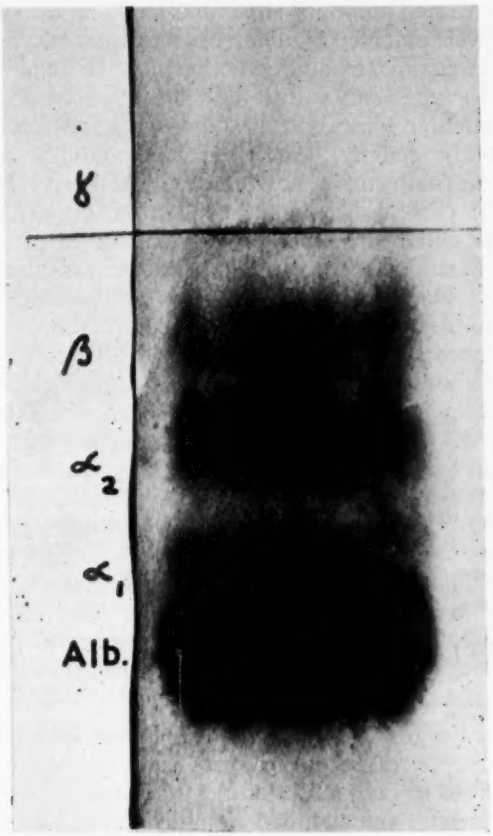

FIG. 3.—Paper electrophoresis (November, 1956), 24 weeks after beginning of treatment with gamma globulin.

Agammaglobulinaemia or Hypogammaglobulinaemia. On inspection the original paper electrophoresis which led to the diagnosis in M.S. suggested a complete absence of gamma globulin (Fig. 1a) but when the paper was examined with a photoelectric densitometer a trace of gamma globulin was revealed (Fig. 1b). Dr. R. A. Kekwick confirmed this by electrophoretic analysis but Dr. P. G. H. Gell was unable to detect any gamma globulin by his immunochemical technique. Other methods of estimation showed varying but small amounts of gamma globulin.

When the earlier cases of this syndrome were described, gamma globulin was considered to be totally absent from the serum and the syndrome was designated 'congenital agammaglobulinaemia'. In recent cases more critical methods of analysis have

shown small amounts of gamma globulin, although the levels obtained by different techniques vary.

The gamma globulin fraction may be separated electrophoretically into several sub-fractions (Cann, Brown and Kirkwood, 1949), each of which has antibody activity, but their precipitability with different antigens varies (Zinneman, Hall and Heller, 1954). This may possibly explain the disparity of values obtained by different methods of estimation. and Martin (1956) considers that the variation of levels of gamma globulin may be because the methods are estimating different sub-fractions. By the more critical methods of analysis, Good (1956) has demonstrated small amounts of gamma globulin in cases originally classified as agammaglobulinaemia. Although Good (1956) suggests that the popular usage of the term 'agammaglobulinaemia' be retained, it would be more accurate to adopt the term 'congenital idiopathic hypogammaglobulinaemia' until such time as the mechanism underlying this disorder is more fully understood, the term 'agammaglobulinaemia' being reserved for those cases in which there is no gamma globulin detectable in the serum by the more critical methods of analysis.

The Congenital Nature of the Syndrome. Deficiency or absence of serum gamma globulin has been described in both adults and children and occurs as a congenital and acquired condition. The transient hypogammaglobulinaemia of early infancy is a physiological phenomenon which under normal circumstances is of no clinical significance. The serum level of gamma globulin in full-term infants at birth is similar to that of the mother but falls to a minimum level at the age of 3 months (Orlandini, Sass-Kortsak and Ebbs, 1955). Thereafter it gradually rises, the normal adult level being approximated by 2 years of age.

Even though an infant is born with the inability to form its own gamma globulin and antibodies, sufficient of both of these may be transferred from the mother before birth to protect the infant from infection during the first few months of life. In the case reported here the onset of recurrent infections did not occur until the age of 8 months. This can be explained by the fact that up to this time a sufficiency of transferred gamma globulin was still present. Martin (1956) endorses this opinion.

We regard our case as congenital although the deficiency was not proved biochemically until the age of 3 years. It is interesting, however, that a year earlier her serum proteins were estimated because of suspected oedema and that at this time the total serum globulin was low (total serum protein 5·2 g. %, albumin 4·0 g. %, globulin 1·2 g. %). Electrophoresis was not carried out on this occasion but it seems likely that the low total globulin was due to deficiency of the gamma fraction.

The Occurrence of the Syndrome in Females. The diagnosis of congenital hypogammaglobulinaemia is based mainly on the fact that the onset of infections was in infancy or early childhood. The earlier reported cases diagnosed on this basis were all males, and Janeway, Apt and Gitlin (1953) have postulated that the syndrome is inherited as a sex-linked recessive trait. The occurrence of the syndrome in females does not necessarily disprove this hypothesis, but there are probably two distinct groups of congenital hypogammaglobulinaemia. The first of these is confined to males, familial and inherited as a sex-linked recessive trait, and the second group, in which females may be affected, is inherited by a different genetic pattern in a similar way to 'haemophilia' in females or possibly arising as a result of a mutation. Hypogammaglobulinaemia has been reported in females under the age of 1 year (Harris and Schick, 1954; Homolka and Mydlil, 1955). These cases are probably infants in whom there has been an exaggeration of the normal physiological fall in serum gamma globulin. The agammaglobulinaemia in an 8-week-old girl, who died of generalized vaccinia following smallpox vaccination (Keidan, McCarthy and Haworth, 1953), was considered by Good and Mazzitello (1956) to be probably a pathological extension of the physiological hypogammaglobulinaemia of infancy. We have observed a premature infant with marked hypogammaglobulinaemia and susceptibility to respiratory infections of a transitory nature. This gives rise to a third group of cases in which the transient physiological hypogammaglobulinaemia is of such degree as to decrease the infant's resistance to infections. The low levels of serum gamma globulin would in these cases be of clinical significance for a transitory period, but the levels would return to normal later. This may be of particular importance in the case of premature infants, and further study is necessary to determine whether there is a critical level of serum gamma globulin below which susceptibility and lowered resistance to infections occurs.

In reviewing the literature it is clear that the nature of the recurrent infections and the organisms responsible may vary, but nearly all the male congenital cases have a history of recurrent major respiratory infections and our case is similar in this respect. The importance of considering hypogammaglobulinaemia in both male and female children who

suffer from recurrent infections cannot be overstressed.

Haematological Changes and Hepatosplenomegaly. The leucocyte count (see Table) was consistently low, the total ranging from 4,300 to 5,100 per c.mm. during her infection-free periods. Even at the height of the infections the highest total count obtained was 9,100 per c.mm. The differential counts suggest that deficiency of both circulating polymorphs and lymphocytes was responsible for the low total counts but there was no consistent lymphopenia or neutropenia, there being considerable variation in the differential counts on different occasions. Leucopenia has frequently been described in hypogammaglobulinaemia, and failure of leucocytosis during infections is well recognized. The explanation remains obscure but Rosecan, Trobaugh and Danforth (1955) have suggested that it may be caused by a lack of some component of gamma globulin which is necessary for the elaboration of the leucocytosis-promoting factor isolated by Menkin (1950). If this is accepted then the leucopenia is an essential part of the hypogammaglobulinaemia syndrome in children. However, we are of the opinion that the leucopenia in M.S. is more likely to be a secondary phenomenon. A leucocytosis of over 20,000 cells per c.mm. was discovered in a 3-year-old girl with hypogammaglobulinaemia without splenomegaly (Rubie, 1956) and the findings in our case suggest that the leucopenia and splenomegaly may be related.

A feature of particular interest in our case was the presence of hepatosplenomegaly. Enlargement of the spleen has been described previously in cases of hypogammaglobulinaemia (Grant and Wallace, 1954, Rohn, Behnke and Bond, 1955; Good and Mazzitello, 1956), and the suggestion has been put forward by Grant and Wallace that it represented a reactive hyperplasia of the reticulo-endothelial system. The reticulo-endothelial cells of the liver and spleen both play an important part in the complex process of antibody formation and they are indirectly involved in the production of the gamma globulin fraction.

In M.S. the spleen was definitely enlarged at the time of her first infection at the age of 8 months. The splenomegaly can hardly be dismissed as 'the result of her recurrent infections', neither can the hepatomegaly be explained on these grounds, and in the absence of any evidence of hepatic dysfunction we regard the hepatosplenomegaly as a reactive hyperplasia. This theory is supported by the fact that since she began treatment with gamma globulin the spleen and liver have both receded and the spleen is no longer palpable.

We have already referred to the possible association of the leucopenia and splenomegaly, and suggest that the leucopenia may be due to secondary hypersplenism. Another possible explanation is that the recurrent infections caused depression of the leucopoietic elements of the bone marrow. The improvement in the leucocyte count after treatment

TABLE

RESULTS OF SOME HAEMATOLOGICAL INVESTIGATIONS RELATED TO PATIENT'S STATE OF HEALTH

Date	Age	State of Health	Temperature (°F.)	W.B.C. per c.mm.	Polymorphs	Lymphocytes	Monocytes	Eosinophils	Haemoglobin	Reticulocytes
5. 1.54	9½ mth.	Bronchopneumonia and left otitis media	104	8,300	49	43	8		60	1·2
20. 1.54	10 mth.	Relapse of pneumonia	105	7,200	31	63	5	1	60	1·2
1. 3.55	23½ mth.	Well	Normal	4,300	51	40	9		64	—
14. 4.55	2 yrs. 1 mth.	Exacerbation of otitis media and purulent rhinitis	101·3	9,100	—	—	—		50	—
26. 5.55	2 yrs. 2 mth.	Infection not responding to penicillin. Started on terramycin		4,300	34	54	12		50	0·6
31. 5.55		Infection controlled. Well		4,300	31	64	5		56	—
24. 8.55	2 yrs. 5 mth.	Very well		4,500	60	36	4		76	2·0
8.12.55	2 yrs. 9 mth.	Bronchopneumonia and otitis media	104	8,100	—	—	—		78	3·0
28. 3.56	3 yrs.	Upper respiratory infection and chronic otorrhoea		5,800	57	35	7	1	66	—
12. 4.56	3 yrs. 1 mth.	Bronchopneumonia, otitis and purulent vaginitis	103	7,000	68	27	5		70	—
23. 4.56		Relapse of pneumonia	101	7,200	62	35	2	1	64	—
2. 5.56		Exacerbation of otitis media and purulent rhinitis	101	8,700	67	30	3		70	—
14. 6.56	3 yrs. 3 mth.	Well	Normal	6,400	47	44	8	1	68	0·6
25. 7.56	3 yrs. 4 mth.	No infection	Normal	5,900	—	—	—		76	1·0
17. 9.56	3 yrs. 6 mth.	Recovering from poliomyelitis	Normal	8,400	—	—	—		76	—
9.10.56		Well	Normal	8,000	62	30	8		84	—
29.10.56	3 yrs. 8 mth.	Recovering from tonsillitis	100·2	6,200	75	17	8		80	—
6.11.56		No infection localized	100	5,300	71	22	7		76	—

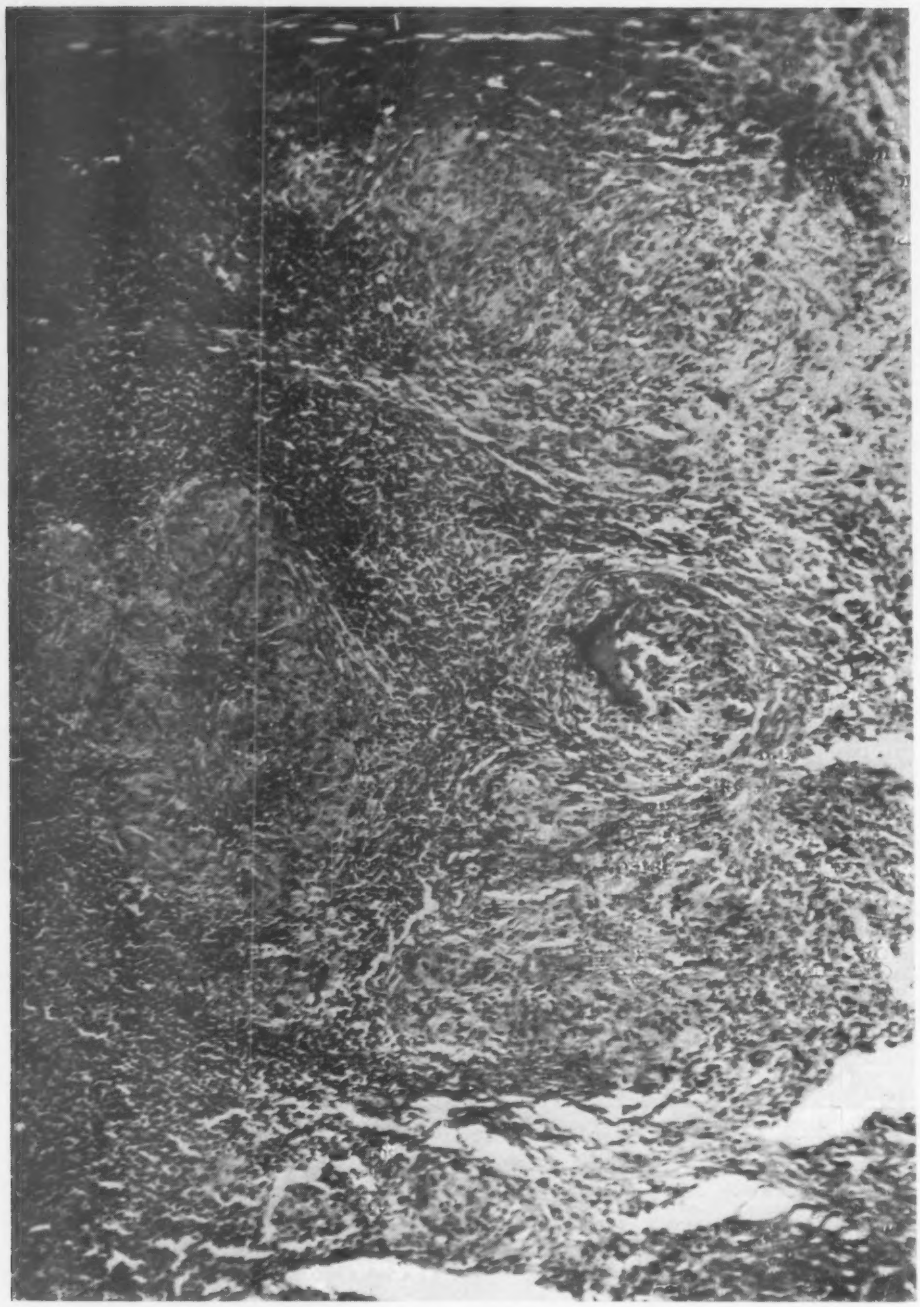

FIG. 4.—Photomicrograph of section of cervical lymph node.

would support either theory, but up to the time of writing we have not had the opportunity to study the leucocyte response to any proved major bacterial infection.

So far we have not discussed the behaviour of the haemoglobin. The haemoglobin values before treatment frequently revealed a moderate anaemia, the red cells showing on some occasions slight anisocytosis, microcytosis and hypochromia. The colour index when this was estimated was in the region of 0·92. The anaemia was not influenced by oral iron therapy and on two occasions blood

transfusions were considered necessary. The hypoplastic reaction of the bone marrow suggests that the anaemia was secondary to the recurrent infections. There was never any significant reticulocytosis and investigations never showed any evidence of haemolysis. Since the administration of gamma globulin the haemoglobin level has remained within normal limits.

The Histological Findings in a Lymph Node. Good (1954, 1955) described the absence of plasma cells from bone marrow and lymph nodes in hypogammaglobulinaemia. He studied the response of the marrow and lymph nodes to antigenic stimulation and found no evidence of plasma cell formation associated with deficient antibody formation in cases of hypogammaglobulinaemia.

A cervical lymph node removed from M.S. was reported as showing a complete absence of plasma cells and distortion of the follicular pattern. In addition some areas were very suggestive of a tuberculous or sarcoid lesion. Examination of Ziehl-Neelsen stained sections failed to reveal any evidence of tubercle bacilli. Mantoux tests (1 in 1,000) carried out when she was 10 months, 2 years 1 month, and 2 years 9 months of age were negative and she is still 'Mantoux negative' at a dilution of 1 in 10. It is difficult to explain the findings of areas in the sections which have the appearance of a tuberculous lesion as being caused by tuberculous infection in view of the negative Mantoux reactions unless deficiency of gamma globulin is responsible for failure of 'conversion'. Elphinstone *et al.* (1956) report a child in whom tuberculous infection occurred after the symptoms of hypogammaglobulinaemia had begun, and in whom conversion of the Mantoux was observed. The Mantoux, 1 in 10,000 in their case, was still positive three years later after the diagnosis of 'agammaglobulinaemia' had been established. The results of Mantoux tests in previously reported cases of congenital hypogammaglobulinaemia have not always been recorded and further study is necessary to establish definitely the behaviour of the Mantoux reaction in this syndrome. Our case gives no history of known contact with tuberculosis and there has never been any reason to suppose that she had a tuberculous cervical adenitis. Although the appearance of the lymph node sections suggests tuberculosis it seems unlikely that the lesion was caused by the tubercle bacillus. The absence of plasma cells and disorganization of the follicular pattern are the histological findings in lymph nodes from cases of congenital hypogammaglobulinaemia (Martin, 1957) but the presence of a granulomatous lesion is an unusual feature.

Zinneman *et al.* (1954) reported a case of acquired agammaglobulinaemia in a 30-year-old female with splenomegaly, leucopenia and anaemia, in whom biopsy of lymph nodes and liver revealed the presence of epithelioid cell granulomas without necrosis. In this case splenectomy was performed for hypersplenism and the spleen also showed numerous granulomas. They considered a probable diagnosis of Boeck's sarcoid and that the agammaglobulinaemia was secondary. It is possible that these lesions may be a histological feature in some cases of congenital or acquired hypogammaglobulinaemia or alternatively they may be the result of infection by some unknown agent. A primary diagnosis of sarcoidosis might have been considered in our case if the deficiency of serum gamma globulin had not been detected earlier.

The Circulating Antibody Levels. There is strong evidence to suggest that the circulating antibodies in man are produced by the plasma cells (Good, 1955). Most of the antibodies and isohaemagglutinins are found in the gamma globulin fraction of the plasma proteins (Cohn, Oncley, Strong, Hughes and Armstrong, 1944) and deficiency of antibody production, associated with absence of plasma cells, is an essential feature of the hypogammaglobulinaemia syndrome. No significant amounts of any of the antibodies estimated were present in the serum of M.S. before treatment with gamma globulin. Antibody formation following antigenic stimulation has not been studied in detail but we did, however, have the opportunity to observe her clinical and immunological response to anterior poliomyelitis.

Response to Anterior Poliomyelitis. This infection occurred 14 weeks after the beginning of treatment when she was receiving 750 mg. of gamma globulin weekly. This gamma globulin was known to contain antibodies to types I, II and III poliomyelitis viruses, but despite this she had a severe paralytic illness. This does not necessarily raise doubts as to the value of gamma globulin in poliomyelitis prophylaxis, for in M.S. its administration may well have prevented a more severe or even fatal illness, but it seems reasonable to suppose that larger doses of gamma globulin are required to effect prophylaxis in cases of hypogammaglobulinaemia.

Before treatment no neutralizing antibody to any of the three types of poliomyelitis virus was detectable in a 1 in 4 dilution of her serum. Type I poliomyelitis virus was isolated from the faeces

during the paralytic phase of the illness but there was subsequently no significant rise in the type I antibody titre. Eight weeks after the onset of infection, antibodies to all three types of virus were detected in her serum at a dilution of 1 in 10.

This equal rise of the antibody levels to all three types of virus is probably due to the administration of gamma globulin over a long period, and suggests that she was unable to produce any antibodies of her own, for one would expect to find a very high antibody titre in a normal child eight weeks after infection.

Summary

The first case of congenital idiopathic hypogammaglobulinaemia in a girl in England is described, and her progress during the first six months of treatment with gamma globulin is reported.

She is aged 3 years 8 months and has a history of recurrent infections since the age of 8 months; shows deficient antibody formation and a failure of immunological response to antigenic stimulation by type I poliomyelitis virus.

A cervical lymph node exhibits the characteristic feature of absence of plasma cells, and the finding of changes resembling a tuberculous or sarcoid lesion are discussed.

The significance of associated leucopenia, anaemia and hepatosplenomegaly are discussed.

The clinical and immunological response to anterior poliomyelitis, occurring during the fourteenth week of treatment with gamma globulin, is commented on.

Attention is drawn to a pathological extension of the normal physiological hypogammaglobulinaemia of infancy and its possible significance in prematurity.

The reasons for preferring the term 'congenital idiopathic hypogammaglobulinaemia' to 'agammaglobulinaemia' are given and the importance of considering the diagnosis of hypogammaglobulinaemia in both female and male children with a history of recurrent infections is stressed.

We wish to thank Dr. R. I. Mackay for permission to publish this case, and for his help and advice; Professor N. H. Martin for his helpful advice and criticism and for the slides and photomicrograph of the lymph node and the classical electrophoretic analysis; Dr. P. O. Williams for his interest and cooperation; Dr. R. A. Kekwick and Dr. P. G. H. Gell for some of the gamma globulin estimations and Dr. F. O. MacCallum for the estimations of the antibody levels and isolation of the poliomyelitis virus. We also thank Dr. G. J. Crawford and his staff for the pathological investigations, particularly Mr. F. Warburton for the paper electrophoresis and photographs in Figs. 1 and 3; Dr. Hall of Ladywell Isolation Hospital for cooperation; Mrs. J. Harrison for secretarial assistance and the nursing staff of Hope Hospital, Salford, for their sympathetic care of M.S. during her periods in hospital.

References

Arnaud-Battandier, R., Cabannes, R., Legendre, E. and Sarfaty, R (1955). *Pédiatrie*, **10**, 880.
Bruton, O. C. (1952). *Pediatrics*, **9**, 722.
Cann, J. R., Brown, R. A. and Kirkwood, J. G. (1949). *J. biol. Chem.*, **181**, 161.
Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L. Jr. and Armstrong, S. H. Jr. (1944). *J. clin. Invest.*, **23**, 417.
Delaitre, R. and Fonty, P. (1955). *Bull. Soc. méd. Hôp. Paris*, **71**, 239.
Elphinstone, R. H., Wickes, I. G. and Anderson, A. B. (1956). *Brit. med. J.*, **2**, 336.
Good, R. A. (1954). *A.M.A. J. Dis. Child.*, **88**, 625.
—— (1955). *J. Lab. clin. Med.*, **46**, 167.
—— and Mazzitello, W. F. (1956). *Dis. Chest.*, **29**, 9.
—— and Zak, S. J. (1956). *Pediatrics*, **18**, 108.
Grant, G. H. and Wallace, W. D. (1954). *Lancet*, **2**, 671.
Harris, J. R. and Schick, B. (1954). *J. Mt Sinai Hosp.*, **21**, 148.
Homolka, J. and Mydlil, V. (1955). *Csl. Pediat.*, **10**, 362.
Janeway, C. A. (1954). Summary of Seminar on Gamma Globulin. International Children's Centre (Paris, 1954).
——, Apt, L. and Gitlin, D. (1953). *Trans. Ass. Amer. Phys.*, **66**, 200.
Keidan, S. E., McCarthy, K. and Haworth, J. C. (1953). *Archives of Disease in Childhood*, **28**, 110.
Kulneff, K., Pedersen, K. O. and Waldenström, J. (1955). *Schweiz. med. Wschr.*, **85**, 363.
Martin, N. H. (1956). Personal communication.
—— (1957). In *Lectures on the Scientific Basis of Medicine*, Vol. 5. London.
Menkin, V. (1950). *Newer Concepts of Inflammation*, 1st ed., No. 70. Springfield, Illinois.
Orlandini, O., Sass-Kortsak, A. and Ebbs, J. H. (1955). *Pediatrics*, **16**, 575.
Rohn, R. J., Behnke, R. H. and Bond, W. H. (1955). *Amer. J. med. Sci.*, **229**, 406.
Rosecan, M., Trobaugh, F. E. and Danforth, W. H. (1955). *Amer. J. Med.*, **19**, 303.
Rubie, J. (1956). Personal communication.
Schick, B. and Greenbaum, J. W. (1945). *J. Pediat.*, **27**, 241.
Thompson, W. H., McQuarrie, I. and Bell, E. T. (1936). *Ibid.*, **9**, 604.
Zinneman, H. H., Hall, W. H. and Heller, B. I. (1954). *J. Amer. med. Ass.*, **156**, 1390.

CHRONIC NEUTROPENIA

BY

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Kostmann (1956) has drawn attention to the existence of a state of chronic neutropenia which may account for recurrent infections in certain children. This state of neutropenia is distinct from that occurring in leukaemia, in toxic states, in infectious diseases, or as a feature of cyclic neutropenia. Kostmann studied six children of whom three died of overwhelming infection before the age of 6 months, and one at the age of 3 years. The remaining two, who were less severely affected, were both alive four years later, but in one the granulocytes in the blood had increased, and in the other there had been no blood counts from the age of 5 months. A study of the families of these children showed that eight other children had died in infancy with a history suggesting agranulocytosis. In one family in which there had been much inbreeding, one branch showed one affected child who had been fully investigated and three elder children who had presented a similar picture; three other branches each showed an affected child who had been fully investigated, and in each of three further branches of the same family a child had died with the same clinical picture. In two other families the parents were closely related. These findings led Kostmann to suggest that the disease was due to a recessive gene and to label these cases 'infantile genetic agranulocytosis'.

There are no other reports of this disease occurring in more than one member of a family. Fanconi (1941) described two infants aged 7 months in whom the granulocytopenia was associated with mild recurrent infections over a period of several months, but in whom recovery eventually took place. Hotz (1941) described agranulocytosis in a girl of 4 months who had suffered from furuncles at the age of 2 weeks. Her blood count was normal two and a half years later. Tobler and Buser-Plüss (1942) described agranulocytosis in a girl of 10 months who had a history of infections from the age of 3 weeks. She was under observation for six months, but her further progress is not recorded. Salomonsen (1948) described another single case, a child of 9 months, in whom granulocytopenia persisted for one and a half years, gradually decreasing after one year. Ström (1949) described a child of 15 months with granulocytopenia for 10 months, but in this case the picture was somewhat different in that the patient had recurrent exanthemata.

The case reported here is another example of the condition and is of interest as the granulocytopenia still persists at the age of 4 years 3 months.

Case Report

Caroline was admitted to the medical ward of the Royal Aberdeen Hospital for Sick Children on November 10, 1954. She was then 23 months old, the second child of healthy parents. Apart from respiratory infection her brother, aged 4 years, had been healthy. She had always been prone to skin sepsis. At the age of 3 days she developed septic spots on the scalp; at the age of 1 month an axillary abscess was incised and she had a paronychia at the same time. She was treated with penicillin and chloramphenicol. At 3 months a preauricular abscess was incised and treatment was with chloramphenicol; at 13 months she suffered from multiple abscesses including a parotid abscess and a submandibular abscess which was incised. Treatment on that occasion was chlortetracycline, sulphadiazine and penicillin. A blood count then showed total white cells 9,500 (neutrophil polymorphs 5%, eosinophils 30%, lymphocytes 55%, monocytes 8%, Türk cells 1%, atypical lymphocytes 1%) but the significance of the low neutrophil count was overlooked. At 18 months of age she developed a staphylococcal infection of the skin which persisted for three months; at 20 months she developed otitis media which was treated with penicillin, and for four months before admission she had had a persistent cough which had become worse two days before admission.

On admission she was not acutely ill but her breathing was distressed. Examination of the chest suggested a right upper lobe pneumonia and a radiograph showed that the right upper and mid zones were opaque and that there were scattered opacities throughout both lungs suggesting bilateral bronchopneumonia. Treatment with sulphadiazine in doses of 0·5 g. six-hourly was started but discontinued after three doses when the blood

count showed 7,400 white cells (neutrophil polymorphs 0%, eosinophils 2%, basophils 1%, lymphocytes 50%, monocytes 44%, Türk cells 3%). As the child remained afebrile, no further treatment was given then.

Investigations

Investigations. The Mantoux test (1 in 1,000 old tuberculin) was negative. No tubercle bacilli were cultured from fasting gastric juice inoculated in guinea-pigs.

A normal amount of gamma globulin in the blood was shown by electrophoresis on two occasions (November 19, 1954, and May 14, 1955).

BONE MARROW (November 23, 1954). Premyelocytes 11·5%, n. myelocytes 3·5%, e. myelocytes 2%, m. metamyelocytes 11%, e. metamyelocytes 6·5%, n. polymorphs 0·5%, e. polymorphs 0·5%, lymphocytes 30·5%, monocytes 20%, plasma cells 7·5%, early normoblasts 2%, intermediate normoblasts 0·5%, late normoblasts 2·5%, megakaryocytes present and producing platelets.

BONE MARROW (December 3, 1954). Myeloblasts 0·3%, premyelocytes 7·0%, n. myelocytes 2·7%, e. myelocytes 3·0%, n. metamyelocytes 2·7%, e. metamyelocytes 7·7%, n. polymorphs 0·3%, e. polymorphs 2·0%, lymphocytes 43·7%, monocytes 12·3%, plasma cells 2·3%, proerythroblasts 1·3%, early normoblasts 2·7%, intermediate normoblasts 2·0%, late normoblasts 8·7%.

BLOOD COUNTS. White blood counts in the patient's family were as follows:

Mother. White blood count 7,400 (n. polymorphs 82%, lymphocytes 15%, monocytes 3%).

Father. White blood count 10,500 (n. polymorphs 56%, eosinophils 5%, basophils 2%, lymphocytes 26%, monocytes 11%.)

Brother. White blood count 3,500 (n. polymorphs 56%, eosinophils 6%, lymphocytes 33%, monocytes 5%).

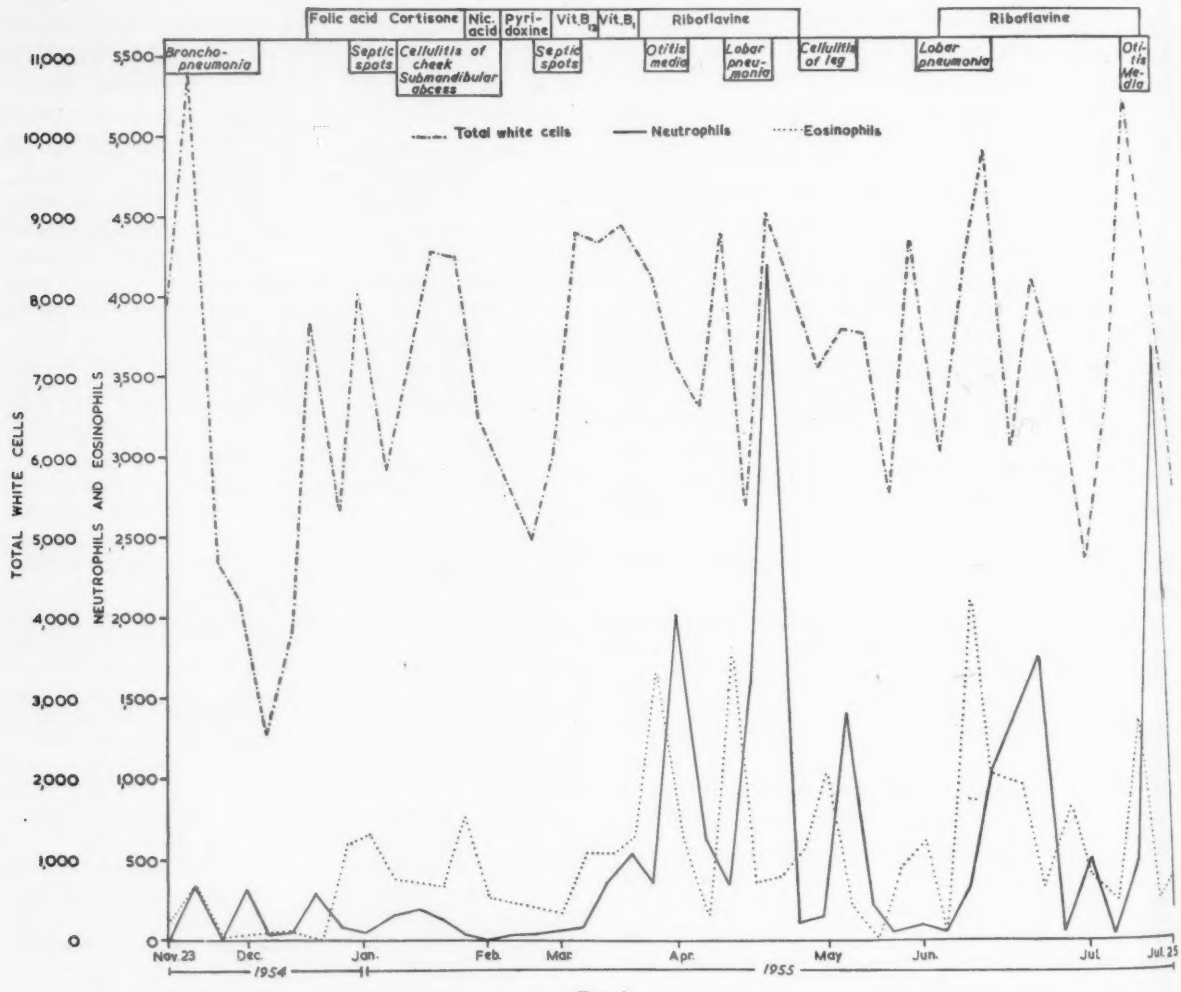

FIG. 1.

Throughout Caroline's stay in hospital 93 blood counts were done at frequent intervals. The accompanying chart shows a selection of those counts and their relation to treatment and to infections.

Infections included bronchopneumonia, two attacks of lobar pneumonia in which the upper lobe of the right lung was the affected area, two attacks of otitis media, cellulitis of a leg, cellulitis of the face accompanied by a submandibular abscess, and recurrent septic spots.

The various substances given in an attempt to raise the neutrophil count were folic acid, 10 mg. three times a day for 17 days; cortisone 75 mg. per day for three days followed by 50 mg. per day for 10 days and withdrawn over a further four days; nicotinic acid 120 mg. daily for 10 days; pyridoxine 100 mg. daily for 10 days, followed by 200 mg. daily for six days; four doses of 1,000 micrograms vitamin B_{12} over a period of 12 days; 100 mg. vitamin B_1 daily for 10 days; riboflavine 30 mg. daily for one period of 36 days; and for another period of 46 days. None of these substances produced and maintained a rise in neutrophils.

Caroline was discharged from hospital on July 25, 1955, and has been seen on nine occasions since then, the last time in March, 1957. The white cell counts have varied from 2,200 to 7,600: neutrophil polymorphs were absent when she was last seen, and on two other occasions, while on the other six occasions the neutrophil counts varied from 100 to 1,300.

Discussion

When this child was first seen, the possibility of granulocytopenia being due to the toxic effect of sulphadiazine was considered, particularly as the blood count previously recorded also followed treatment with sulphadiazine. Her history of recurrent infections and her subsequent progress, however, suggest that the granulocytopenia was not caused by sulphadiazine and had existed from birth.

Kostmann's suggestion that this condition might be familial led to investigation of the whole family. The parents were not related and there was no history of relatives either dying in early infancy or suffering from recurrent infections. Blood counts on her father, mother and brother failed to show any neutropenia.

Despite the low neutrophil count the total white blood cells rarely fell to very low levels although readings as low as 2,200 were recorded. This agrees with the findings in most of the reported cases. Bone marrow examination showed maturation arrest of the granulocyte series. Kostmann found this in some of his cases, and as cell culture experiments with bone marrow had shown that activation and maturation of cells were obtained when cysteine or normal serum was added, he gave cysteine orally, subcutaneously and intravenously to one child but without any effect. Caroline had been discharged from hospital before this work became known. As she lived 35 miles away regular blood counts were impossible, and it was considered that re-admission to hospital with its risks of infection in order to try the effect of cysteine was not justifiable. While she was in hospital folic acid, cortisone, pyridoxine, vitamin B_{12}, vitamin B_1 and riboflavine were all administered in turn without effect. At first it seemed that riboflavine might be producing a rise in neutrophil polymorphs, as counts of 4,200, 3,600, 2,100 and 2,000 were recorded while she was on that treatment, but the count fell on one occasion to 80, and on another to nil while she was still on riboflavine. On every occasion the rise in neutrophils was preceded by an infection, on two occasions otitis media and on two occasions pneumonia, but infections occurred at other times without any subsequent rise in neutrophils. The highest neutrophil counts were always preceded by a rise in eosinophils, a feature that has not been noted in any of the cases reported in the literature.

The problem of management of this child was great and it was decided that she should have constant treatment with antibiotics. On discharge from hospital she was having a daily dosage of 300 mg. chlortetracycline which was later changed to the same dosage of tetracycline hydrochloride. Minor skin sepsis has occurred from time to time: she has had mild respiratory infections, and radiographs of the chest still show some opacity in the upper zone of the right lung, but she has had no severe illness.

The cases reported in the literature were either not followed up to this age or the blood count had returned to normal, but in this child there is no indication of improvement.

Summary

A case of chronic neutropenia associated with recurrent infections from birth is reported in a girl now 4 years 3 months old.

Folic acid, cortisone, pyridoxine, vitamin B_{12}, vitamin B_1 and riboflavine were all given without producing a permanent rise in neutrophil polymorphs.

On constant treatment with antibiotics the child has remained free from severe infections for almost two years.

I should like to thank Professor John Craig and Dr. Norman S. Clark for their encouragement and help in presenting this case, and the Haematology Department, Aberdeen Medical School, for their numerous blood counts.

References

Fanconi, G. (1941). *Ann. paediat.* (*Basel*), **157**, 317.
Hotz, A. (1941). *Z. Kinderheilk.*, **62**, 529.
Kostmann, R. (1956). *Acta paediat.* (*Uppsala*), **45**, Suppl. 105.
Salomonsen, L. (1948). *Ibid.*, **35**, 189.
Ström, J. (1949). *Ibid.*, **38**, 590.
Tobler, W. and Buser-Plüss, E. (1942). *Ann. paediat.* (*Basel*), **159** 258.

WHEAT GLUTEN AND COELIAC DISEASE

BY

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The relationship between the development of symptoms of coeliac disease and the feeding of wheat flour was first established by Dicke (1950) in Holland. Dicke, Weijers and van de Kamer (1953) confirmed this association by feeding experiments using a quantitative biochemical method in the form of a long-term fat balance to determine the appearance and disappearance of steatorrhoea. Anderson, Frazer, French, Gerrard, Sammons and Smellie (1952), working independently, also demonstrated this correlation and confirmed that gluten or the protein fraction of wheat flour was the deleterious agent causing symptoms and steatorrhoea.

The symptomatology of coeliac disease is largely dependent on inadequate absorption of foodstuffs which occurs when gluten is included in the diet and wheat and rye flour proteins are the only cereal proteins which have been shown conclusively to induce this malabsorption. Several groups of workers have investigated the possible mechanism by which gluten acts deleteriously. The following hypotheses have been suggested and examined: first, 'the allergic hypothesis' or sensitivity of these patients to wheat gluten, and secondly, the 'enzyme hypothesis' or alteration in the ability of these patients to digest and absorb gluten. Wheat and rye gluten are different from other cereal proteins in their chemical and physicochemical constitution in that they contain more glutamic acid and proline and can form a type of gel which enables them to be used in breadmaking. Little is known of the chain structure of the gluten molecule and the particular arrangement of peptides in the molecule, but the peptide pattern is probably associated with the gel property. A difference in peptide structure of wheat and rye gluten, together with a difference in the extra- or intracellular enzyme pattern of the coeliac patient might therefore be responsible for the development of symptoms in this disease.

This paper presents some investigations to test these hypotheses and critically assesses other work in this field and makes suggestions concerning future experimental approaches. Although no definite conclusions are drawn it is felt that a record of these investigations will avoid repetition by others or stimulate further ideas.

Allergy to Wheat Gluten

Although an occasional patient with coeliac disease is noted to react to the taking of gluten very quickly with diarrhoea and vomiting, in the great majority symptoms appear slowly and recede slowly on removal of the offending substance from the diet, and the reaction does not clinically resemble allergy. In none of 28 patients with true coeliac disease studied during the past four years, has there been any history of asthma or finding of eosinophilia in the blood. In only seven patients was there any family history of allergic disease. One child showed eczema which did not clear on removal of gluten from the diet, although the symptoms of coeliac disease did.

Intradermal skin tests using a 2% gluten solution were carried out on eight patients by one of us (C.M.A.) in England, and on six patients in the present study, with completely negative results.

The suggestion that this reaction to gluten might be an allergic one cannot be upheld by skin testing, therefore.

Digestion and Absorption of Wheat Gluten

First, digestion of gluten by the extracellular enzymes in the intestinal tract was examined. Secondly, the effect of various digestive products or fractions of gluten, prepared and fed to patients, was tested with especial emphasis on the search for a peptide with a high content of glutamic acid and proline. The absorption of gluten digestive products was then considered, with defective mucosal intracellular enzymes in mind, and blood peptide and amino-acid patterns examined before and after the administration of test doses of gluten.

Extracellular Enzymes. Although it has often been shown in patients with coeliac disease that the

pancreatic enzymes estimated in duodenal fluid are present in normal quantities, and that gastric juice contains pepsin, the action of these enzymes on wheat gluten itself has not been recorded.

Gastric and duodenal fluids and succus entericus were obtained by intubation from four coeliac patients and allowed to act successively on a 2% gluten substrate. The *p*H in each case was adjusted to that required by the enzyme and the mixture incubated at 37° C. for a minimal time of three hours for each enzyme. A blank test was made with boiled enzymes and gluten. At the end of the test gluten could be precipitated from the blank on the addition of acetic acid whereas in the tube containing the incubated enzymes it had been digested. The biuret test was negative after the action of the digestive enzymes. Digestion with enzymes from normal children gave a similar result.

This method of testing was not considered to be very sensitive but attempts at identification of digestive products by paper chromatography were foiled by the many interfering amino-acids and peptides in the gastric and duodenal fluids themselves.

From these results it was felt that there was no gross difference in the primary digestion of gluten in normal children and patients with coeliac disease.

Effect of Various Fractions of Gluten. Testing the effect of gluten and any fractions of gluten on patients with coeliac disease in order to obtain a definite quantitative answer involves the performance of a continuous or intermittent fat balance for a considerable number of weeks (Anderson *et al.*, 1952). First, the patient must recover and the fat absorption become normal by removal of gluten from the diet. When the fraction is fed, a negative result cannot be inferred unless absorption remains normal during at least three to four weeks. If a positive result is obtained, this should be checked by a return to normal when the offending fraction is withdrawn. All this involves considerable periods in hospital for the patient and much tedious nursing and laboratory work. Consequently few patients can be studied in this way. However, the following fractions were tested each on one patient by studying the fat excretion in the stools continuously during the period of feeding.

PHOSPHOLIPID FRACTION. This fatty fraction is associated with gluten and can be extracted by fat solvents and separated as an oily substance. Feeding of this to one patient did not produce any increase in fat excretion during one month. However, on subsequent feeding of the gluten from which the phospholipid had been extracted, fat excretion rose to 6 g. a day in two weeks (normal less than 4 g. a day), showing that the toxic property was still present.

TRYPTIC DIGEST. Gluten was digested in bulk with pancreatic extract and the product dried and fed to a patient with coeliac disease. The composition of the digest was checked by two-dimensional paper chromatography and shown to be a mixture of peptones and peptides. Feeding of this digest caused a recurrence of steatorrhoea, fat excretion rising to 5·4 g. daily after being stabilized at a level of 3·5 g. daily. Recovery occurred again after withdrawal of the digest.

The tryptic digest was further separated by dialysis through a cellophane membrane. When this dialysate, that is the fraction containing the smaller peptide molecules, was fed for three weeks to a boy, mild clinical symptoms were reproduced and fat excretion rose from 3 to 7 g. per day.

It seemed apparent from these experiments that the peptides from gluten could still harmfully affect patients with coeliac disease.

AMINO-ACID DIGEST. One of us (C.M.A.) working in England had fed an amino-acid digest of gluten (prepared by Bengers Ltd.) to one child with no increase of fat excretion during one month. Therefore complete hydrolysis of gluten seemed to have removed its toxicity. Glutamic acid alone was also given by mouth to a child for one month, in amounts equivalent to that contained in 9 g. of gluten per day, but no increase of fat excretion occurred.

GLUTAMIC ACID-CONTAINING PEPTIDES. A fractionation of the bulk tryptic digest was attempted, hoping to isolate peptides containing relatively large amounts of glutamic acid.

Separation with increasing quantities of ethanol was unsuccessful, and a fractionation involving the separation of calcium salts was then made by Foreman's method (1914). Chromatograms of the portion separating at an alcohol concentration of 50 to 95% showed a peptide containing a greater proportion of glutamic acid and proline than the other fractions. It was also more homogeneous. After removal of the calcium this peptide was fed to a patient but no ill effects resulted. However, it was felt to be an unsatisfactory experiment as larger dosage may have been needed because the peptide could have been altered by manipulation and converted to a non-reactive molecule. Van de Kamer and Weijers (1955) have shown that deamination of whole gluten can make it innocuous and this may have occurred in our manipulations.

Blood Peptides and Amino-acids. As the testing of gluten fractions by feeding and fat balance is so

tedious and time consuming, requiring large quantities of the substance, and long stay of the patient in hospital, other methods for testing the fate and action of ingested gluten were sought.

It was thought that a study of the blood amino-acid and peptide pattern might be informative. Three normal children and three patients with coeliac disease were given a 30 g. dose of gluten and blood taken two hours later. The blood peptides and amino-acids were studied by two-dimensional paper chromatography. The serum proteins were removed by alcohol and the smaller molecules were fractionated on a Dowex resin (50) column. There was no detectable difference either before or after acid hydrolysis in the chromatogram patterns of the two groups. However, this method could not indicate quantitative differences in peptides, nor variation in the arrangements of the peptide molecules.

Blood Glutamine Estimations. Fasting blood glutamine levels and the rise in values after a test dose of gluten were estimated by the method of Seegmiller, Schwartz and Davidson (1954). This applies microdiffusion for the estimation of glutamine after the specific action of Krebs' glutaminase (1948). The ammonia evolved was measured by nesslerization.

In seven control children fasting levels averaged 7·0 mg. % with a range of 4·9 to 8·7. The level in 15 coeliac patients was 5·5 mg. % with a range of 2·9 to 8·4. Therefore no significant difference in fasting levels was shown.

Working independently in Holland, Weijers and Van de Kamer (1955) studied blood glutamine curves using the Prescott-Waelsch method. They considered that, following a test feeding of gliadin (350 mg. per kg.) coeliac patients showed an average increase of 100% in the fasting blood glutamine level, whereas the increase for normals averaged 15%, the highest level being 40%.

In a small series of patients (Table 1) we studied blood glutamine levels two hours after a test dose of 700 mg. of gluten per kilogram of body weight. It can be seen in each case and in the average figures that the rise in blood glutamine is three times higher in coeliac patients than in controls. This small series gives similar findings to those of the Dutch workers, but the increase is of a lesser degree. The test dose was 700 mg. of gluten per kilogram which corresponded to the 350 mg. dose of gliadin (the 70% alcohol-soluble fraction of gluten) used by Weijers and van de Kamer.

It was thought that this increase in blood glutamine might be used as an index of the toxicity of various gluten fractions, but results were disappointing. Treated cases were used, and comparable doses of fractions given. However, these convalescent patients gave inconsistent results and not always an abnormally high rise of blood glutamine.

Discussion

While this work has been proceeding, colleagues in both Holland and England have been pursuing very similar investigations. There has for a number of years been a free interchange of ideas between these groups and trends in the work of each group have brought them to the idea that the basic defect in the coeliac child might be a specific alteration or absence of an enzyme, probably a peptidase normally produced in the intestinal mucosal cells. Certain pieces of evidence produced by each group lend some support but no absolute proof to this conception.

Clinically some features favour the conception of a specific developmental defect in this disease. True coeliac disease seems to be a condition occurring in a small number of children when they are exposed to rather specific dietary conditions, that is, when wheat or rye protein is included in their diet. They are healthy before gluten is included in the diet and they react to this protein always or at least until adult. The effect is shown predominantly as an alteration of small intestinal absorbing function, but certain generalized changes are also observed, such

TABLE 1

BLOOD GLUTAMINE VALUES BEFORE AND AFTER A TEST DOSE OF 700 MG. OF GLUTEN PER KILOGRAM BODY WEIGHT

Blood Glutamine (mg. per 100 ml. blood)					
Controls			Coeliac Patients		
Fasting	Two Hours after Test Dose	% increase	Fasting	Two Hours after Test Dose	% Increase
7·5	8·1	8	4·7	7·3	55
4·9	6·5	32	2·9	4·7	62
7·0	8·7	34	7·1	7·0	72
8·7	11·7	34	3·2	8·0	128
		Average=27			Average=79

as hypotonia and a change in temperament with depressive features. All these things are reversible or reproducible by the subtraction or addition of gluten to the diet. The children are predominantly fair haired and probably all of European descent. These clinical features suggest that the group has some common developmental abnormality which shows up when the offending substance is fed.

The present work produces evidence to discount the idea that this reaction to gluten is an allergic one. Other work has been directed towards finding the specific fraction of gluten which is toxic and which by its identification might give some idea of the possible underlying defect.

Van de Kamer and Weijers (1955) drew attention to the high content of glutamine in wheat and rye gluten but demonstrated that glutamine itself was not toxic to a case of coeliac disease. They went further and showed that by boiling gliadin with 1N HCl a product was obtained in which glutamine was deaminated. This had lost its toxicity and they concluded that glutamine in a bound form was probably the toxic factor.

Frazer (1956), describing the work of his colleagues with gluten fractions, finds that a water-soluble peptide fraction obtained following tryptic digestion possesses the toxic properties of the original gluten. Digestion of this peptide fraction with an extract of pig's intestinal mucous membrane causes disappearance of the toxic effect. They concluded that the effect of gluten was brought about by a glutamine-containing peptide that was probably digested by an enzyme present in the normal intestinal wall but absent in the coeliac child, and postulated a specific enzyme deficiency. They thought that such a concept could explain the observation of van de Kamer and Weijers regarding the reaction of the coeliac child to bound glutamine and the higher content of glutamine in the blood.

The present work has shown that digestion of gluten to the peptide stage appears to take place normally in coeliac children. Complete digestion to the amino-acid stage renders it harmless. However, various intermediate fractions, such as a tryptic digest and a water-soluble dialysate of this, are still active. This seems to indicate that a peptide is probably the harmful substance. The abnormally high increase in blood glutamine following a dose of gluten or gliadin observed by us and Weijers and van de Kamer (1955) indicate that a peptide-containing glutamine is the toxic fraction.

These features suggest that a specific mucosal peptidase which might deaminate the peptide is absent from the small intestine. However, it is also possible that the removal of glutamine peptides from the bloodstream by the liver may be impaired and that the primary defect lies there and not in the bowel wall. In order to clarify this, further study of the peptidase enzyme pattern of the bowel mucosa and the liver is necessary and also the testing of specific peptides which have glutamine in the terminal position.

Regarding blood glutamine levels this estimation has been suggested by Weijers and van de Kamer (1955) as a diagnostic test for gluten sensitivity but they point out that in some cases results were inconsistent and in a personal communication felt that this test was not always reliable. Our results also suggest unreliability, especially in mild or convalescent patients. In coeliac children, all tests which depend on the rate of absorption from the gut during a period of hours are of doubtful value owing to the generalized upset in the absorbing mechanism of these children. The use of this type of test diagnostically is probably not justified.

Summary

No evidence of an allergic reaction to wheat gluten can be demonstrated in patients with coeliac disease.

Gluten exerts a harmful effect in these patients whether given as a whole protein or as predigested peptide.

After a dose of gluten, blood glutamine rises to a higher level in coeliac patients than in normal children.

The concept that the toxic effect of gluten is due to a peptide containing glutamine is discussed and a specific intracellular enzyme deficiency postulated.

We wish to thank Mrs. A. Cahn of the Biochemistry Department, Melbourne University, for preparing the 'phospholipid fraction'.

REFERENCES

Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G. and Smellie, J. M. (1952). *Lancet*, **1**, 836.
Dicke, W. K. (1950). *Coeliakie*. M.D. Thesis. Utrecht.
——, Weijers, H. A. and Kamer, J. H. van de (1953). *Acta paediat. (Uppsala)*, **42**, 34.
Foreman, F. W. (1914). *Biochem. J.*, **8**, 463.
Frazer, A. C. (1956). *Proc. roy. Soc. Med.*, **49**, 1009.
Kamer, J. H. van de and Weijers, H. A. (1955). *Acta paediat. (Uppsala)*, **44**, 465.
Krebs, H. A. (1948). *Biochem. J.*, **43**, 51.
Seegmiller, J. E., Schwartz, R. and Davidson, C. S. (1954). *J. clin. Invest.*, **33**, 984.
Weijers, H. A. and Kamer, J. H. van de (1955). *Acta paediat. (Uppsala)*, **44**, 536.

PALPABILITY OF THE LIVER AND SPLEEN IN INFANTS AND CHILDREN

BY

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The extent to which the liver and spleen project below the costal margin in infants and children does not seem to be generally known. This study was undertaken to define the normal range of palpable projection of the liver edge below the costal margin in different age groups and so help to resolve some of the conflicting views on the subject. The number of subjects in whom the spleen was palpable was also recorded.

Material and Methods

Three hundred and seventeen apparently healthy infants and children (166 males and 151 females) between birth and 16½ years were examined. A history of pathological jaundice or recent illness excluded any child. The subjects were found in nurseries, for newborn and premature babies, in orphanages and industrial schools.

The Liver. Measurements were made in the mid-clavicular line to the nearest half-centimetre with a short ruler, the zero mark of which was flush with the end of the ruler, this being firmly pressed against the costal margin. Measurements were made with the subject supine, the head being supported on a low pillow; they were made during the hour before meals, and in the case of some infants where abdominal relaxation was not otherwise obtained, during the first minutes of a feed. All measurements were, whenever possible, made in the end-expiratory position, that is during the momentary pause following quiet expiration. When the liver edge coincided, with or receded behind, the costal margin in the end-expiratory position, projection was recorded as zero. The liver edge was palpated with the left hand from the patient's left side; this method was rational, at least for those who find it easiest to palpate a pyloric or colonic tumour in the sub-hepatic region in this way.

The Spleen. It was found easiest to palpate the spleen with the right hand from the patient's right side.

No measurements of the projection of the spleen below the costal margin are given, the organ being recorded as palpable whether only palpated during quiet inspiration or otherwise.

Finding the liver or spleen in the first place is easiest when the fingers are kept stationary, movement of the diaphragm being relied on to push the viscus against the fingers.

Results

The Liver. The results are summarized in the table. The liver edge projected on average a little less than 2 cm. in the mid-clavicular line in full-term infants in the newborn period (taken for convenience here to be the first 21 days); the range was 0·5 to 2·5 cm. In premature infants, the average projection was slightly less, 1·6 cm., range 1 to 2·5 cm. From 21 days to 6 months, from 6 to 12 months and from 12 to 18 months, the average projection was 1·5, 1·8 and 1·5 cm. respectively, the range being 0 to 3·5 cm. in each group. From 1½ to 5½ years the average projection was 1 cm., range 0 to 3·5 cm., from 5½ to 10½ years it was 1 cm., range 0 to 3 cm., and from 10½ to 16½ years it was 0·85 cm., range 0 to 4 cm.

As no marked difference between the sexes was apparent, the figures for males and females were added; there was a slight trend for both liver and spleen to project more in older boys. In 10 subjects (3·4% of all examined) it was not found possible to palpate the liver edge accurately, usually due to inadequate relaxation, and these cases were discarded. The liver edge was found to be most nearly parallel with the right costal margin during the first year, during which time it was also most readily palpable in the right mid-axillary line and to the left of the midline. The edge of the left lobe of the liver can frequently be followed as far as the left mid-clavicular line in infancy, but beyond this age it becomes progressively more unusual to palpate it to the left of the subcostal notch. The amount of the anterior surface of the liver uncovered by the ribs is thus relatively greatest in the newborn period. The notches in the liver edge corresponding to the gall bladder and ligamentum teres were occasionally palpable, particularly with good relaxation of the abdominal wall in infants, the latter notch being defined with more difficulty due to the intervening

rectus muscle. In the supine subject, the plane of the projecting anterior surface of the liver is approximately horizontal in most instances, that is to say, parallel to the contiguous anterior thoracic and abdominal walls. From about the fifth to the tenth year, in those subjects in whom the projection of the liver was greatest, it was frequently found that the anterior surface shelved downwards, the fingers needing to be pressed deeply into the abdomen to find the edge, which could on occasion be felt to ride up over the fingers on inspiration.

The Spleen. The spleen was palpated below the costal margin in 11·1% of the series; it was felt that attempts to measure the projection would be of little value. Projection tended to be less in the older age groups, when in fact it was frequently difficult to be sure whether there was any significant projection in the end-expiratory position, the spleen, however, being readily palpable during inspiration. The spleen was palpated in 13·5% of newborn infants, 12·7% of those from 21 days to 1½ years, 7·2% of those from 1½ to 10½ years and 16·6% of those from 10½ to 16½ years. This last figure of 16·6% in the 10½ to 16½ group may be due either to chance, or to some unrecognized infective or other factor, since the majority of those in this group in whom the spleen was palpated were boys from one institution, their liver projection being also in the higher ranges.

Discussion

Cruchet and Sérégé (1908) studied 160 subjects aged from birth to 18 years by palpation of the liver edge in axillary, nipple and mid lines. Their figures show the average projection of the liver edge in the nipple line at birth to be 4·7 cm. (two cases only), falling abruptly to 0·4 cm. during the second year (eight cases only), remaining at 2 cm. from 5 years to 12 years and becoming impalpable at 14 years.

Nelson's *Pediatrics* (1954) states that 'in the newborn infant, the liver edge may be as much as 5 cm. below the costal margin in the right M.C.L.' Abt's *Pediatrics* (1923) summarizes the findings of Cruchet and Sérégé (1908) thus:

> 'They found that the inferior margin of the right lobe rapidly approaches the right costal margin until the middle of the second year, when it again begins to descend until the middle of the second period of childhood. After this time a second period of ascent occurs, ending in adolescence with the right liver margin at the usual normal adult position.'

This statement has been repeated in almost identical words in Brenneman's *Practice of Pediatrics* and in Gaisford and Lightwood's *Paediatrics for the Practitioner* (1953).

Zamkin (1926) studied 2,100 apparently normal infants and children by palpation of the liver and spleen, the measurements being recorded in terms of the author's fingerbreadth and then transcribed into centimetres. He found the percentage of palpable livers to vary from 100% in the first year to 50% from 10 to 12 years, and of palpable spleens to vary from 43% in the first year to 10% from 10 to 12 years. The liver projected below the costal margin between 2·5 and 5·5 cm. in the mid-clavicular line in 77% of subjects from 10 days to 1 year and in 74% of children from 2 to 4 years; these figures are in conflict with those of the present study and a projection of the liver below the costal margin in

TABLE

Age	No. of Subjects	Projection of Liver Edge below Costal Margin in Mid-clavicular Line				Palpable Spleen
		Average in cm.	Range in cm.	S.D.	Zero Projection	
0–21 days 1,250 to 2,500 g.	11	1·59	1 to 2·5	0·53	0	2
0–21 days 2,500 to 3,500 g.	13	1·77	0·5 to 2·5	0·50	0	2
0–21 days 3,500 to 4,500 g.	13	2·04	1·5 to 2·5	0·31	0	1
21 days to 6 months ..	23	1·46	0 to 3·5	0·96	4	4
6 to 12 months	18	1·75	0 to 3·5	1·10	2	1
12 to 18 months ..	13	1·46	0 to 3·5	1·16	3	2
2 years*	22	1·13	0 to 3·0	0·97	8	3
3 „	14	1·00	0 to 3·5	0·80	6	1
4 „	25	0·64	0 to 2·0	0·58	14	0
5 „	20	0·98	0 to 3·0	0·98	9	1
6 „	17	0·76	0 to 3·0	1·00	9	2
7 „	11	1·14	0 to 2·5	0·85	3	1
8 „	15	0·90	0 to 2·5	0·58	6	2
9 „	13	1·12	0 to 2·5	0·75	3	0
10 „	16	1·00	0 to 3·0	0·94	6	1
11 „	10	1·05	0 to 3·0	0·91	3	2
12 „	11	1·18	0 to 4·0	1·24	4	2
13 „	14	0·86	0 to 3·0	0·81	5	2
14 „	17	0·86	0 to 2·0	0·72	10	2
15 „	10	0·70	0 to 2·0	0·78	5	3
16 „	11	0·68	0 to 2·0	0·69	5	1

* '2 years' includes all children between 1½ and 2½ years, '3 years' all those between 2½ and 3½ years, etc.

the mid-clavicular line of more than 3·5 cm. in the newborn would in my experience indicate hepatic enlargement. Zamkin's measurements for older children were 3·5 cm. or less in 79% of 5-9-year-old children and 84% in 10-12-year-old children. These measurements are more in accordance with those of the present series.

The marked retraction of the liver edge between birth and the second year described by Cruchet and Sérégé and repeated by other authors was based on few observations and does not conform with the findings in the present study.

Whilst the use of the fingerbreadth as a measure of projection is a reasonable approximation for a single observer for most clinical purposes, I have found that the lateral diameter of the terminal joint of the index finger may vary from 1·3 cm. in a petite house physician to 2·0 cm. in two robust members of the surgical staff.

That the spleen was palpated in 11·1% of this series may be considered surprising, but it coincides with my impressions over a number of years. The incidence in the 10½ to 16½ year group was, however, higher than anticipated, and has been commented upon. More success in finding the splenic edge in infants will be achieved if its frequently axillary situation is remembered.

Summary

In 317 apparently healthy infants and children, the projection of the liver edge below the costal margin, the topography of the palpable liver surface and the palpability of the spleen were studied.

When measured in the end-expiratory position, the mean projection of the liver edge below the costal margin in the right mid-clavicular line was slightly less than 2 cm. in the newborn infant, 1·6 cm. in the premature infant, 1·6 cm. during the remainder of the first year, 1 cm. from 1½ to 10½ years and 0·85 cm. from 10½ to 16½ years.

It was possible to palpate the spleen in 11·1% of all these subjects, in 13·5% of newborn babies, in 12·7% during the remainder of the first year and in 7·2% of those from 1½ to 10½ years.

Suggestions for standardizing the procedure for simple clinical measurements of the projection of the liver are made.

I wish to thank Dr. Alex Russell, O.B.E., for his most helpful criticism of this paper; I believe that it was he who first drew my attention to the ease with which the liver can be palpated from the patient's left side; also Prof. M. J. Newell for his help with the statistics.

I wish to thank the following for their kindness in allowing me to examine children under their care: The Master and Dr. W. Kidney, Coombe Maternity Hospital, Dublin; Dr. S. MacLaverty, Regional Hospital, Galway; the Bon Secours Sisters, the Sisters of Mercy, the Sisters of Charity of St. Vincent de Paul and the Irish Christian Brothers.

References

Abt, I. A. (ed.) (1923). *Pediatrics*. Philadelphia.
Brennemann, J. *Practice of Pediatrics*, Vol. 3, p. 4. Hagerstown, Maryland.
Cruchet, R. and Sérégé, H. (1908). *Gaz. hebd. Sci. méd. Bordeaux*, 29, 158.
Gaisford, W. and Lightwood, R. (1953). *Pediatrics for the Practitioner*. London.
Nelson, W. E. (1954). *Textbook of Pediatrics*, 6th ed. Philadelphia.
Zamkin, H. O. (1926). *Arch. Pediatrics*, 43, 169.

B.C.G. TUBERCULIN

BY

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It is well known that after Bacille Calmette-Guérin (B.C.G.) vaccination the degree of allergy as shown by the tuberculin test is of a lesser order than that after infection with virulent tubercle bacilli. For this reason it may be necessary to perform several successively stronger tuberculin tests up to 100 units of old tuberculin (Mantoux 1/100) before a positive post-vaccination test is obtained. Several tests, however, are inconvenient to patients and physicians alike. In addition, a test with 100 tuberculin units may well give rise to non-specific false positive reactions.

Several investigators abroad have reported that a tuberculin prepared from the B.C.G. substrain of tubercle bacilli is a more sensitive indicator of tuberculin allergy in vaccinated persons (Bluhm, 1949; Hagberg, 1950; Lind and Holm, 1943; Magnusson, Lithander and Hagberg, 1949; Ruziczka, 1952a and b; Quaiser, 1954). As we required a sensitive quantitative test to evaluate the antigenic properties of several batches of newly introduced freeze-dried B.C.G. vaccines of British manufacture (Lorber, Hart, Farmer and Muggleton, 1956; Lorber, Farmer and Muggleton, 1957), we decided to conduct a controlled trial of B.C.G. tuberculin as one of the post-vaccination tests.

Preparation of B.C.G. Tuberculin

The B.C.G. (Copenhagen strain) tuberculin was grown at 37° C. for eight weeks on Sauton's medium containing 4% glycerol. The cultures were heated for three hours at 100° C. after which the growth was collected by filtration and discarded. The clear filtrate was reduced to 10% of its original volume by low pressure distillation. An equal volume of 20% aqueous trichloracetic acid solution was then added slowly with continuous stirring and the solution kept at 4° C. overnight. The precipitate which had formed was collected by centrifuging and washed three times with distilled water. The precipitate, suspended in distilled water, was then dialyzed against running tap water for six hours and then against frequent changes of distilled water for one week at 4° C. The suspension was then redissolved by the addition of the minimum necessary quantity of sodium hydroxide in solution and the *p*H then readjusted to 7·0 with hydrochloric acid. After sterilization by filtration through a Seitz filter, 0·5% phenol was added.

The concentrated tuberculin solution was then standardized against international standard purified protein derivative (P.P.D.) tuberculin by the method of Long, Miles and Perry (1954). For use, the concentrated stock solution was diluted in 10% glycerol, 0·5% phenol solution to contain 10 units in 0·1 ml. The solution was filled into 2·0 ml. glass ampoules.

The B.C.G. tuberculin was used in the following forms:

(1) A solution of 1/1000 for intradermal use by the Mantoux technique, containing 10 T.U. per 0·1 ml. dose.

(2) A solution containing 10,000 T.U./ml. for percutaneous use with the multiple puncture (Heaf, 1951) technique; and

(3) A tuberculin jelly for percutaneous use containing 60,000 units of B.C.G. tuberculin. (This is the same concentration of tuberculin as is used in the standard old tuberculin jelly, ' tradermin ', of Allen and Hanbury.)

Present Investigation

(*a*) **Type of Subjects.** In order to assess the value of B.C.G. tuberculin in vaccinated subjects it was also necessary to ascertain that it does not give false positive reactions in non-tuberculous and in unvaccinated persons and that it gives reliable positive reactions in persons with active or inactive tuberculosis. For this reason controlled clinical trials were carried out on the following groups of subjects, numbering 987 in all.

(1) Uninfected and unvaccinated children and young adults (191 subjects).

(2) Children with active tuberculous infections (80 subjects).

(3) Young adults (students and nurses) with inactive or latent tuberculous infections (74 subjects).

(4) Infants, children and young adults (642 subjects) who had been vaccinated with either the liquid Danish B.C.G. vaccine or with one of five freeze-dried vaccines of different viable cell counts. These had been vaccinated a few weeks to several years before they were tested with B.C.G. tuberculin.

(*b*) **Methods of Testing.** By far the largest number were tested by the intradermal (Mantoux) route. Concurrent tests were performed in 987 subjects as follows:

(1) Five hundred and seventy-six subjects received by

Mantoux technique 10 T.U. of B.C.G. tuberculin compared with 10 T.U. of old tuberculin.

(2) One hundred and fifty-one subjects received by Mantoux technique 10 T.U. of B.C.G. tuberculin compared with 100 T.U. of old tuberculin.

(3) One hundred and seven subjects received 10 T.U. of B.C.G. tuberculin intradermally compared with P.P.D. tuberculin (100,000 T.U. per ml.) by multiple puncture test (Heaf, 1951).

(4) Seventy-six subjects received B.C.G. tuberculin (10,000 T.U.) compared with P.P.D. tuberculin (100,000 T.U.) by multiple puncture test.

(5) Seventy-seven subjects received B.C.G. tuberculin jelly (60,000 T.U. per g.) compared with O.T. tuberculin jelly (60,000 T.U. per g.) percutaneously without the use of flour paper.

An induration of 6 mm. or more was taken as positive in the case of the Mantoux tests, and four papules or more in the case of the jelly tests. The criteria of Heaf were used for the assessment of the multiple puncture tests. Dr. P. W. Gifford performed all the tests on adults.

Results

(1) Tuberculin-negative Children. There were 191 subjects who were considered to be tuberculin negative as a result of the tests. In 187 of these (98%) no reaction whatever followed either test. The details of the tests are set out in Table 1. The

TABLE 1
TUBERCULIN TESTS IN TUBERCULIN NEGATIVE SUBJECTS

Test 1	Test 2	Number Tested
B.C.G. (T) 10 T.U. ..	O.T. 10 T.U.	93
B.C.G. (T) 10 T.U. ..	P.P.D. (Heaf)	53
B.C.G. (T) (Heaf) ..	P.P.D. (Heaf)	22
B.C.G. (T) jelly ..	O.T. jelly	23
Total ..		191
No reaction to either test ..		187
Reaction below minimum requirement		4

remaining four gave some reaction but below the minimal criteria of a positive test. One, a child of 13, had a discoloration of 17 mm. in diameter but no induration at the site of the B.C.G. tuberculin injection (10 T.U.) while there was no reaction at all to 10 units of old tuberculin. When retested, there was no reaction to either antigen and after B.C.G. vaccination there was no untoward or accelerated development at the vaccination site. Two other children, aged 3 and 10, gave similar results. The fourth case was an adult who was tested with 10 units of B.C.G. tuberculin intradermally and who showed an induration of 3 mm. in diameter 72 hours later. A concurrent multiple puncture test with P.P.D. tuberculin produced papules which were just palpable. The test was repeated and the same result was obtained.

There were 104 other subjects who gave no reaction to 10 units of B.C.G. tuberculin but had no concurrent tests with old tuberculin.

It can be concluded, therefore, that B.C.G. tuberculin in the three forms used did not give false positive reactions when compared with established methods of tuberculin testing with O.T. or P.P.D.

TABLE 2
TUBERCULIN TESTS IN TUBERCULOUS SUBJECTS

Test	Number Tested	Number Positive	Average Induration (mm.)
(*a*) *Children*			
B.C.G. (T) 10 T.U.	54	54	22
O.T. 10 T.U.	54	52	16
B.C.G. jelly ..	26	26	—
P.P.D. jelly ..	26	24	—
(*b*) *Adults (inactive cases)*			
B.C.G. (T) 10 T.U.	53	53	—
P.P.D. (Heaf)	53	52	—
B.C.G. (T) (Heaf)	21	20	
P.P.D. (Heaf)	21	21	

(2) Tuberculous Children. Concurrent tests with B.C.G. tuberculin and with O.T. were carried out on 80 children with known recent tuberculous infection. Most of them had uncomplicated primary tuberculosis but 12 cases of miliary tuberculosis or meningitis are included among them. In 54 intradermal tests (10 T.U.) and in 26 the jelly tests were used. A positive result was obtained with B.C.G. tuberculin in all cases. Four children tested with O.T. (two Mantoux tests and two jelly tests) gave a negative result. All four were bacteriologically proven cases of meningitis or miliary tuberculosis. For example, an infant of 4 months of age was tested soon after her admission with miliary tuberculosis and again three months later. The response of 10 units of B.C.G. tuberculin was an induration of 10 and 7 mm. respectively, and to 10 units of O.T. a papule of 2 mm. diameter on the first occasion and no reaction at all on the second occasion.

The average diameter of induration with intradermal B.C.G. tuberculin in 54 children was 22 mm. (range 7-50 mm.) and with O.T. 16 mm. (range 6-27 mm.). In four children the reaction to O.T. was larger, in four they were equal and in 46 the B.C.G. tuberculin gave the stronger reaction.

Of the 26 children tested with the jelly, the reaction produced by the B.C.G. tuberculin was generally more widespread and more definite.

It appears, therefore, that unit for unit the B.C.G. tuberculin gave stronger reactions in tuberculous

children than O.T. and that some children with a low degree of allergy gave negative reactions of O.T. and positive ones to B.C.G. tuberculin.

(3) Adults with Latent or Quiescent Tuberculosis. Among 149 young adults (nurses and students) who underwent routine tuberculin testing 74 gave a positive result. There was no clinical or radiological evidence of active tuberculosis in any of these. Fifty-three had tests with 10 T.U. of B.C.G. tuberculin intradermally and concurrent multiple puncture tests with P.P.D. tuberculin. Unequivocally positive tests were obtained in 52. In the 53rd the B.C.G. tuberculin gave an induration of 15 mm. but there were only just palpable papules with the multiple puncture P.P.D. test. The same result was obtained on repeating the tests.

Twenty-one subjects had concurrent multiple puncture B.C.G. tuberculin and P.P.D. tuberculin tests. The B.C.G. tuberculin contained 10 times fewer units per millilitre than the P.P.D. tuberculin. Twenty gave positive tests to both, but one was negative to B.C.G. and positive to the P.P.D. test. The P.P.D. test gave a stronger reaction in 10, an equal reaction was found in nine, and B.C.G. tuberculin gave a stronger reaction in one.

It is seen, therefore, that among these 74 subjects there was good agreement between B.C.G. tuberculin and P.P.D. tuberculin in 72. In the remaining two one or the other of the two tuberculins gave a negative reaction.

(4) Children and Adults after B.C.G. Vaccination. By far the largest group (642 subjects) were infants, children and young adults who were tested three weeks to several years after B.C.G. vaccination. Of these, 580 infants and children had intradermal tests with 10 units of B.C.G. tuberculin concurrently with either 10 units of O.T. (429 cases) or 100 units of O.T. (151 cases). In addition, 29 children had concurrent jelly tests and 33 young adults had concurrent multiple puncture tests with B.C.G. and P.P.D. tuberculins. All the 33 adults and 203 infants and children had been vaccinated with the Danish liquid B.C.G. vaccine and 406 children had been vaccinated with one of five different batches of freeze-dried B.C.G. vaccine.

The details of the vaccines, the subjects, the time which had elapsed after vaccination and the results of the intradermal tests are fully set out in Table 3. A positive result was obtained with the B.C.G. tuberculin in 567 (97·7%) infants and children. Eight of the 13 negative reactors had been vaccinated with two early batches of freeze-dried vaccine now

TABLE 3

COMPARISON OF RESULTS OBTAINED WITH INTRADERMAL B.C.G. TUBERCULIN AND INTRADERMAL OLD TUBERCULIN AT DIFFERENT STRENGTHS

Vaccine		Subjects	Period after Vaccination	Tuberculin Tests								
				B.C.G. Tuberculin (10 T.U.)			O.T. (10 units)			O.T. (100 units)		
Type	Viability Count per Millilitre (approximate)			Number Tested	Number Positive	Average Induration (mm.)	Number Tested	Number Positive	Average Induration (mm.)	Number Tested	Number Positive	Average Induration (mm.)
Danish	13×10^6	Infants 6–12 weeks	6–12 weeks	157	156 (99·9%)	12·1	96	47 (48·9%)	4·9	62	62 (100%)	12·6
Danish	13×10^6	Contact children	1 yr. or more	46	46 (100%)	18·0	46	34 (73·9%)	9·0	—	—	—
F.D. Batch 50	$0·1 \times 10^6$	1-year-old children vaccinated at birth	1 year	83	83 (100%)	17·0	80	54 (67·5%)	7·0	3	3	19·0
F.D. Batch 93a	11×10^6	Infants 6–12 weeks	6–12 weeks	141	139 (98·6%)	11·1	73	32 (43·8%)	4·1	67	67 (100%)	11·1
F.D. Batch 93a	11×10^6	Children aged 4 months-14 years	3 weeks	13	13 (100%)	15·0	13	10 (76·9%)	10·0	—	—	—
F.D. Batch 77	23×10^6	1-year-old children vaccinated at birth	1 year	111	109 (98·2%)	20·0	92	85 (92·4%)	11·0	19	19 (100%)	23·0
F.D. Batches 42 and 48	Variable	2-year-old children	2 years	29	21 (72·4%)	10·0	29	15 (51·7%)	6·0	—	—	—
				580	567 (97·7%)		429	277·(645%)		151	151 (100%)	

not in use. Of the 429 children tested with 10 T.U. of O.T., only 277 (64·6%) gave a positive result, and of the 151 tested with 100 T.U. of O.T., all gave a positive result. None of the last group had been vaccinated with the early batches of B.C.G. tuberculin.

The average diameter of induration produced by the tests varied according to the type of vaccine used and the interval following vaccination. The lowest average diameter with B.C.G. tuberculin was 10·0 mm. in a small group vaccinated with a weak vaccine and the highest was 20·0 in a group vaccinated with the vaccine of the highest viable count (23×10^6/ml.). The average induration was consistently much lower in each group tested with 10 T.U. of O.T. (4·1-10·0 mm.) and a little higher in those tested with 100 T.U. of O.T. (11·1-23·0 mm.) as compared with the induration produced by 10 T.U. of B.C.G. tuberculin.

Of the 29 children who were tested with the two types of tuberculin jelly, all gave a positive reaction to the B.C.G. tuberculin jelly and only 22 were positive to the O.T. jelly. Of the positive reactors 19 gave strongly positive tests to B.C.G. tuberculin as compared with only two to old tuberculin.

Of 33 adults tested with the multiple puncture technique, all gave positive results to both tests. The B.C.G. tuberculin, whose tuberculin content was one-tenth that of the P.P.D. tuberculin, gave nevertheless stronger reactions in three. In the others the reactions were of equal grade.

Discussion

This investigation shows that B.C.G. tuberculin may be satisfactorily used as a standard tuberculin test to detect tuberculous allergy in infected persons and to exclude tuberculous infection in non-infected persons. In this respect it seems to be as effective as old tuberculin. In fact, in the tuberculous children 10 units of B.C.G. tuberculin intradermally or the B.C.G. tuberculin jelly gave consistently more positive reactions than the corresponding preparation of old tuberculin. This is particularly valuable in cases of miliary or meningeal tuberculosis, because of the well known anergy in these conditions. Nevertheless, the most important role of B.C.G. tuberculin is the detection of tuberculous allergy in B.C.G. vaccinated children. As has been shown, 10 units of B.C.G. tuberculin by the Mantoux test detected tuberculin allergy in 97·7% of vaccinated children, whereas 10 units of old tuberculin used in the same way and at the same time in the same children only produced a positive reaction 64·5%. Ten units of B.C.G. tuberculin were virtually as effective in showing tuberculin conversion as 100 units of old tuberculin, without the same risk of giving false positive results. Further, a single test with 10 units was sufficient to detect tuberculin allergy in virtually all vaccinated and tuberculous subjects without having recourse to two or more consecutive tests.

Unfortunately relatively little B.C.G. tuberculin was available for the preparation of a tuberculin jelly, which is extravagant in tuberculin content. Nevertheless the findings in 77 children who had concurrent tests with B.C.G. and old tuberculin jelly of identical tuberculin content confirm the results obtained in the much larger series of subjects who were tested with the Mantoux technique. It will be of great interest to investigate a B.C.G. tuberculin jelly on a larger scale once supplies become more plentiful. Now that the quantitative aspects of testing with B.C.G. tuberculin have been established by controlled trials with Mantoux tests, the potential advantages of a tuberculin test which is reliable under all conditions and which does not require any form of injection (or abrasion) are obvious and require further study.

In the 76 adult subjects in whom B.C.G. tuberculin was used by the multiple puncture test, the results were again similar to those obtained by the intradermal or the jelly tests. The P.P.D. tuberculin used in these tests was 10 times more concentrated, yet in half the cases of natural infection the intensity of the reaction following the two tests was equal. In the other half the P.P.D. tuberculin gave the stronger reaction. In the vaccinated subjects there was no appreciable difference in the intensity of the reaction in spite of the difference in the strength of the two tuberculins.

It would be interesting to know whether it is possible to distinguish between naturally or artificially induced tuberculin sensitivity with the help of B.C.G. tuberculin. Although this aspect has not been the primary object of this investigation, it does not appear that this is any more possible with B.C.G. tuberculin than with old tuberculin. Although the average diameter of induration of the Mantoux lesion following the injection of 10 units of B.C.G. tuberculin was larger (22 mm.) in tuberculous than in vaccinated children (10·0 mm.-20·0 mm. according to type of B.C.G. used and the time which elapsed since vaccination), there was such a large area of overlap that an attempt at differential diagnosis on this ground would be unjustified.

In conclusion, in B.C.G. tuberculin we have an effective and reliable agent for the detection of tuberculin sensitivity. It is particularly useful for tests after B.C.G. vaccination, as it appears to be much more potent than old tuberculin when used

in weaker dilutions, thus eliminating the possibility of false positive reactions and the need for several tests. These results fully confirm the findings of those workers abroad whose work has been cited in the introduction. Of course, in these cases B.C.G. tuberculin may measure a specific sensitivity to B.C.G. and a positive reaction does not necessarily mean the presence of immunity against tuberculous infection. As, however, we have no laboratory tests which would measure immunity, this test is the nearest and best we have so far.

Summary

This report deals with an investigation to evaluate a tuberculin, prepared from the B.C.G. organism (B.C.G. tuberculin) on 987 subjects. In all these concurrent tests were performed with old tuberculin or P.P.D. by intradermal (Mantoux), percutaneous (jelly) or multiple puncture tests.

The tuberculin gave no false positive reactions in 191 subjects; it reliably detected tuberculin sensitivity in subjects with active or inactive tuberculosis and dose for dose was a more sensitive indicator of allergy than old tuberculin. Finally, it was a far more sensitive index of tuberculin conversion in B.C.G. vaccinated subjects than the same dose of old tuberculin.

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References

Bluhm, I. (1949). *Acta tuberc. scand.*, Suppl. 21, p. 24.
Hagberg, E. (1950). *Acta paediat. (Uppsala)*, **39**, 461.
Heaf, F. (1951). *Lancet*, **2**, 151.
Lind, P. and Holm, J. (1943). *Acta tuberc. scand.*, **17**, 237.
Long, D. A., Miles, A. A. and Perry, W. L. M. (1954). *Bull. Wld Hlth Org.*, **10**, 989.
Lorber, J., Farmer, P. and Muggleton, P. W. (1957). *Tubercle (Lond.)*, **38**, 227.
——, Hart, C. B. S., Farmer, P. and Muggleton, P. W. (1956). *Tubercle, (Lond.)*, **37**, 187.
Magnusson, J. H., Lithander, A. and Hagberg, E. (1949). *Ann. paediat. (Basel)*, **173**, 253.
Quaiser, K. (1954). *Beitr. Klin. Tuberk.*, **110**, 507.
Ruziczka, O. (1952a). *Öst. Z. Kinderheilk.*, **8**, 67.
—— (1952b). *Wien. klin. Wschr.*, **64**, 158.

THE HYPERSENSITIVITY REACTIONS TO PARA-AMINOSALICYLIC ACID (P.A.S.)

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Para-aminosalicylic acid (P.A.S.) was first used in 1946 for the treatment of tuberculosis by Lehmann (1946). With the exception of nausea and vomiting, which Lehmann himself described, it was at that time thought that the drug was free from side-effects. However, with its increasing use, reports of other toxic reactions began to appear (Nagley and Logg, 1949: Hemming and Stewart, 1949) and there now exists an extensive literature on the subject.

These reactions fall into three groups (Dixon, 1954). First is a natural intolerance to the drug which as many as 58% of patients (Medical Research Council, 1950) experience, whose manifestations (nausea, vomiting and sometimes diarrhoea) appear very soon after starting the treatment.

Secondly, pharmacological side-effects have been described. These consist of hypoprothrombinaemia (Swanson, 1949), hypokalaemia (Cayley, 1950), hypothyroidism (Komrower, 1951) and hyperthyroidism (Tandhanand and Buri, 1956). The alterations in thyroid metabolism are usually associated with the occurrence of a goitre.

Thirdly, there are the hypersensitivity reactions, and these are usually the most serious. Table 1 lists these reactions.

Kniest (1952) has reported an anaphylactic reaction immediately after restarting treatment in two cases that had already shown some allergy to P.A.S., but this should be regarded as an exaggerated version of the normal hypersensitivity reaction.

The present case is reported because it shows so many of the hypersensitivity reactions to P.A.S., and helps to shed some further light on them. In addition, ascites and pleural effusion have not previously been reported as complications of P.A.S. therapy. Furthermore it is the first report of P.A.S. sensitivity following the administration of calcium B-P.A.S.

TABLE 1

THE HYPERSENSITIVITY REACTIONS TO P.A.S.

Fever	Cuthbert (1950)
Skin rashes	Horne (1949)
Exfoliative dermatitis	Cuthbert (1950)
Pruritus	Steel (1952)
Stomatitis	Jeffery *et al.* (1952)
Headache	Hemming and Stewart (1949)
Lachrimation and conjunctivitis	Warring and Howlett (1952)
Blood dyscrasias	
(*a*) Eosinophilia	Dixon (1954)
(*b*) Glandular fever cells	Cannemeyer *et al.* (1955)
(*c*) Agranulocytosis	Muri (1952)
Vasomotor rhinitis	'Any Questions' (1953)
Lymphadenopathy	Cuthbert (1950)
Hepatitis and hepatomegaly	Dixon (1954)
Albuminuria and haematuria	Nagley and Logg (1949)
Transient anuria	Cuthbert (1950)
Anaphylactic shock	Kniest (1952)
Angioneurotic oedema	Cuthbert (1950)
Laryngeal stridor	Warring and Howlett (1952)
Intractable cough	Hemming and Stewart (1949)
Asthma	Gerrits (1951)
Löffler's syndrome	Warring and Howlett (1952)
Pleural effusion Ascites	Present case

Calcium 4-Benzamidosalicylate (Calcium B-P.A.S. 'Therapas')

In an attempt to overcome the high degree of intolerance found when P.A.S. is administered as the normal sodium or calcium salt (in solution, in cachets or in granules), Bavin and James (1953) described this new substance which is insoluble and, perhaps for that reason, tasteless. It is broken down in the body to liberate P.A.S. and benzoic acid. Preliminary reports suggest that calcium B-P.A.S. is therapeutically as effective as the normal salts of P.A.S., and produces intestinal disturbances in a far smaller proportion of cases.

Case Report

The patient, a girl of 7 years, developed primary tuberculosis and was treated with I.N.H. and calcium B-P.A.S. There was nothing relevant in either her previous medical history or in her family history. Her

elder brother (the only sibling) and both her parents were well and showed no evidence of active tuberculous infection: the contact was never found.

For convenience all dates have been related to the day she first received P.A.S. ('P' day, April 24). Fig. 1 illustrates the progress of the case.

31.3.56 (P−24) The patient was seen with a rash on her shins which resembled erythema nodosum.

2.4.56 (P−22) Tuberculin jelly test positive, control negative.

4.4.56 (P−20) Radiological report (1).
Pathological report (1)

5.4.56 (P−19) Erythema nodosum settling slowly. A fairly constant evening pyrexia of 99° F. noted.

20.4.56 (P−4) Radiological report (2)
Pathological report (2)

24.4.56 (P day) In view of the increasing radiological changes, antituberculosis therapy was started, using I.N.H. and 'calcium B-P.A.S.'.

20.4.56 (P+5) A rubella-like eruption appeared during the afternoon but lasted only two hours. Its significance was not appreciated.

12.5.56 (P+18) The eruption recurred, and with it the temperature rose to 101° F. The cervical nodes, especially those in the posterior triangles, were enlarged.

14.5.56 (P+20) For the first time nausea was experienced on taking the B-P.A.S. The dose was reduced with no improvement.

17.5.56 (P+23) The child's condition was much worse, and she looked ill. An irritating morbilliform rash had replaced the rubella-like one and covered the whole body. The conjunctivae were suffused and her eyes were watering. Several small ulcers were present on the buccal mucosa and inside the mouth. The adenitis had increased considerably; not only were all the nodes in the neck enlarged, but also those in the axillae and groin, though the spleen could not be felt (nor could it at any other time). All antituberculosis therapy was stopped on this day.

18.5.56 (P+24) The eyelids and face were swollen and the ankles slightly oedematous. She was complaining of quite severe abdominal pain and on examination the liver edge was palpable and tender. The urine showed the presence of bile salts and pigments, and there was albumin ++ (bed-side analysis).

22.5.56 (P+28) Liver edge palpable three fingerbreadths below the costal margin. Temperature 101-104° F.

23.5.56 (P+29) Pathological report (3)

26.5.56 (P+32) The temperature returned to normal, but the liver was now palpable five fingerbreadths and jaundice could be detected, though it was not at any time very marked.

28.5.56 (P+34) Subjectively the child felt much better but on examination signs were detected in the chest for the first time. The percussion note was

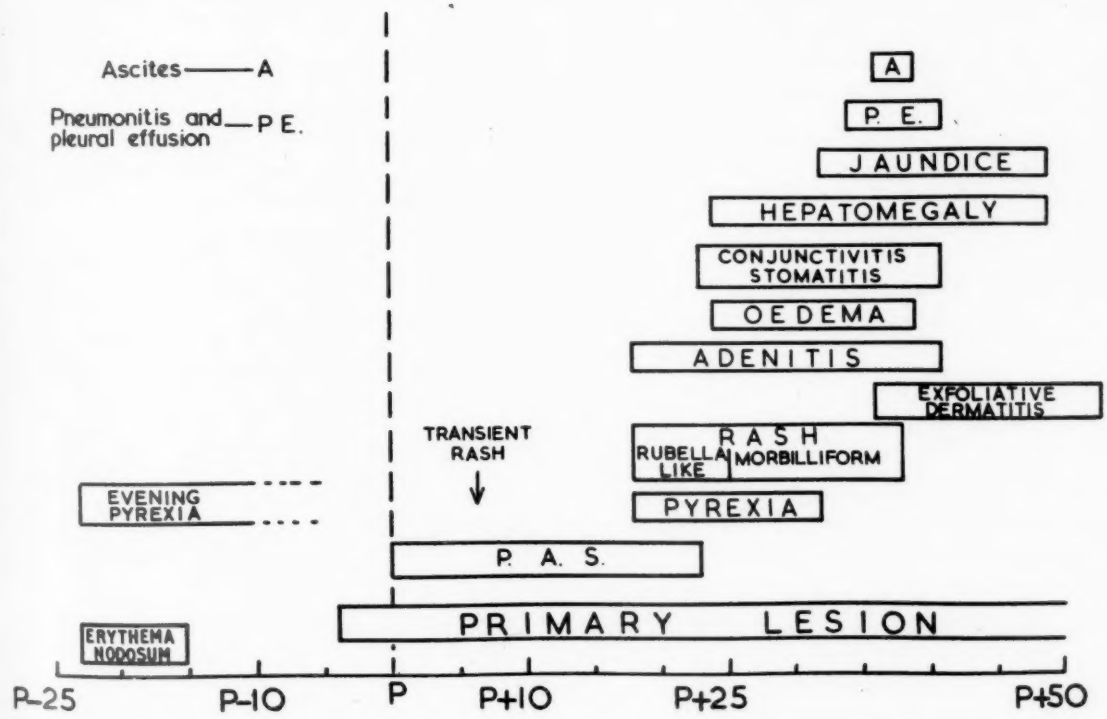

FIG. 1.

FIG. 2.

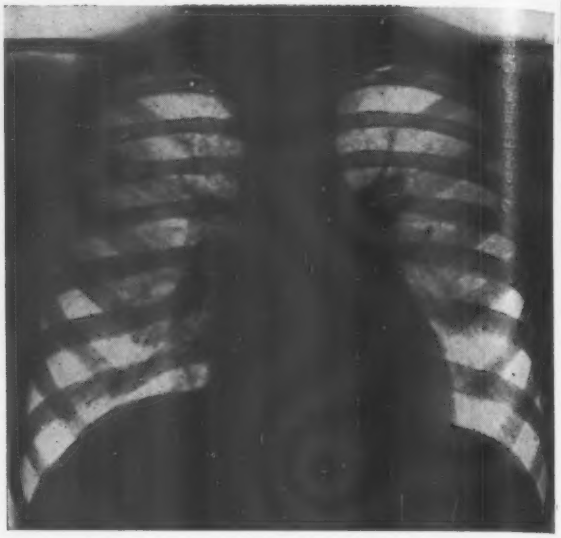

FIG. 3.

dull in the right axilla and air entry was diminished over the right lower lobe.

29.5.56 (P+35) Radiological report (3)
Pathological report (4)

30.5.56 (P+36) Ascites was found. The skin was beginning to peel over both thumbs and thenar eminences as the rash was starting to fade.

2.6.56 (P+39) General condition much improved. Liver edge decreased to two fingerbreadths. Ascites was now no longer detectable. The oedema had subsided. Pulmonary signs were unaltered. The exfoliation was spreading all over the body.

4.6.56 (P+41) The chest was clinically clear. The oral and conjuctival ulcers had settled. The adenitis was subsiding.

5.6.56 (P+42) Radiological report (4)
Pathological report (5)

12.6.56 (P+49) All the signs had disappeared except for the remains of the exfoliative process on the legs.

29.6.56 (P+66) Child clinically very well. Appetite good. Up half day.
Radiological report (5)
Pathological report (6)

14.8.56 (P+112) Gaining weight. Full activity.
Radiological report (6)
Pathological report (7)

11.10.56 (P+140) Radiological report (7)
Pathological report (8)

1.10.56 (P+161) Permitted to return to school.

10.9.57 The child is clinically very well. The primary tuberculosis complex is no longer visible radiologically.

Radiological Reports

(1) 4.4.56 Lung fields clear. Left hilum a little suspicious.

(2) 20.4.56 The left hilar glands are enlarged and there is some consolidation in the apical segment of the lower lobe or in the posterior segment of the upper lobe. The radiological appearances are consistent with the presence of a primary tuberculous complex.

(3) 29.5.56 There is now a small effusion at the right base and some fluid is also present in the intralobar fissure. There may be a little atelectasis above it (Fig. 2).

(4) 5.6.56 The right lung field is now clear and there is no evidence of fluid. The left hilar mass is unchanged (Fig. 3).

(5) 29.6.56 The position of the left hilum has not altered materially.

(6) 14.8.56 Comparison with the previous films shows little change. The left hilar glands are still enlarged.

(7) 11.9.56 The enlarged glands at the left hilum have not altered materially in size in the last month.

Pathological Reports

(1) 4.4.56 Hb 11·2 g. %. W.B.C. 7,600 per c.mm. (5,800 polymorphs, 1,700 lymphocytes, 100 monocytes). E.S.R. 42 mm./hr.

(2) 20.4.56 Hb 12·8 g. %. W.B.C. 13,000 per c.mm. (8,400 polymorphs, 3,900 lymphocytes, 700 monocytes). E.S.R. 41 mm./hr.

(3) 23.5.56 Hb 12·3 g. %. W.B.C. 9,000 per c.mm. (3,500 neutrophils, 500 eosinophils, 5,000 lymphocytes). A few of the mononuclear cells were atypical and resembled those seen in glandular fever.

(4) 29.5.56 Urine: amber yellow. S.G. 1·016, *p*H. 7·0, albumin nil, bile salts nil, glucose nil, bile pigments ++, urobilinogen 1·5 units %, 6 leucocytes and less than 1 R.B.C. per c.mm.

(5) 5.6.56 Hb 12·7 g. %. W.B.C. 13,000 per c.mm. (7,600 polymorphs, 6,300 lymphocytes, 600 monocytes). E.S.R. 24 mm./hr. Urine: bile salts +, bile pigments ++, urobilinogen 1·1 units %. A few of the monocytes were atypical. Paul-Bunnell test was positive to 1:16 only, i.e., negative.

(6) 29.6.56 Hb 13·0 g. %. W.B.C., no abnormal cells seen. E.S.R. 31 mm./hr.

(7) 14.8.56 Hb 13·4 g. %. E.S.R. 15 mm./hr. Stool was solid dark brown, no blood or mucus, no ova or cysts.

(8) 11.9.56 Hb. 13·0 g. %. E.S.R. 5 mm./hr.

Discussion

Jaundice and hepatomegaly are well-known complications of P.A.S. therapy and Dixon (1954) has reviewed the literature. In almost all the cases reported, other toxic symptoms were present; of those cases referred to by Dixon, lymphadenopathy, exfoliative dermatitis, and oedema of the face were common accompaniments as well as eosinophilia which was more often than not part of a generalized leucocytosis. Dixon, however, makes no mention of the presence or absence of 'glandular fever cells'.

A reaction to P.A.S. resembling infectious mononucleosis (glandular fever) was first described by Sjoukes (1952). Warring and Howlett (1952) included this complication in their list and referred to a Veterans Administration report on the subject. Several cases have since been reported by Lichtenstein and Cannemeyer (1953) and these authors (Cannemeyer, Thompson and Lichtenstein, 1955, have elsewhere discussed the haematological changes at greater length. All their eight cases were accompanied by a skin rash which was usually erythematous and macular. Lymphadenopathy was found in half the cases. Two had hepatomegaly (one of which was jaundiced) and blood changes of hepatitis (raised alkaline phosphatase, thymol turbidity, and bilirubin, as well as a positive cephalin flocculation test) were found in most of the cases investigated. Also found in most of their cases was a lymphocytosis—relative or absolute—while the Paul-Bunnell test was always repeatedly negative.

It appears that there is a considerable connexion between the two reactions in that symptoms of both the syndromes are usually found whenever they occur as complications of P.A.S. therapy. The present case is further evidence.

A transitory pneumonitis associated with an eosinophilia (Löffler's syndrome) as one of the hypersensitivity reactions to P.A.S. was first reported by Warring and Howlett (1952). Löffler's syndrome when it is due to other causes has been accompanied by a pleural effusion (Crofton, Livingstone, Oswald and Roberts, 1952) as it was in the present case. It is unlikely that either the pneumonitis or the effusion was tuberculous for both cleared completely in a week. Neither ova nor cysts were found in the stools.

The ascites was also probably due to the 'therapas', for the degree of hepatitis was insufficient to account for it, and there was no splenomegaly.

Stomatitis and conjunctival suffusion together with a puffy face and generalized oedema are typical of a drug fever, and albuminuria is often found in the same condition. The rash, too, which resembled erythema multiforme, can occur with a drug fever, and, as mentioned above, it also often accompanies the hepatitis and 'glandular fever reaction' following P.A.S.

Allergic reactions to P.A.S. therapy are not common in children (Todd, 1953) though they do suffer the same natural intolerance to the drug. Hepatitis does not appear to have been reported previously in a child though Oppe (personal communication) had a case which ended fatally. Both of Kniest's (1952) cases of anaphylactic reaction were in children, the older of whom (aged 12) died from a concomitant flare-up of a tuberculous infection.

Summary

A case is reported of a child treated with P.A.S. who developed hypersensitivity reactions. These reactions included drug fever, lymphadenopathy with 'glandular fever cells' in the blood, hepatitis with jaundice and dermatitis with exfoliation. In addition the child developed Löffler's syndrome with a pleural effusion and had ascites.

I wish to thank Drs. J. Fielding and P. L. Masters for the pathological reports and Drs. T. R. Riley and J. J. Stevenson for the radiological reports.

Considerable advice was received from the St. Mary's Hospital Home Care Department, though, because the patient lived outside the area they cover, she did not come into their scheme. I would like to thank Dr. Lightwood and his team for all their assistance, and in particular I wish to thank Dr. Lightwood for his help in the preparation of this paper. I would also like to thank Dr. B. Kustow, whose patient the child is, for his permission to look after the child, and for his encouragement.

References

'Any Questions' (1953). *Brit. med. J.*, **2**, 296.
Bavin, E. M. and James, B. (1953). *J. Pharm. Pharmacol.*, **5**, 849.
Cannemeyer, W., Thompson, J. R. and Lichtenstein, M. R. (1955). *Blood*, **10**, 62.
Cayley, F. E. de W. (1950). *Lancet*, **1**, 447.
Crofton, J. W., Livingstone, J. L., Oswald, N. C. and Roberts, A. T. M. (1952). *Thorax*, **7**, 1.
Cuthbert, J. (1950). *Lancet*, **2**, 209.
Dixon, W. M. (1954). *Brit. J. Tuberc.*, **48**, 102.
Gerrits, J. C. (1951). *Geneesk Gids*, **29**, 169.
Hemming, M. and Stewart, C. J. (1949). *Lancet*, **2**, 174.
Horne, N. W. (1949). *Ibid.*, **2**, 349.
Jeffery, Borrie, P. and MacDonald, N. (1952). *Brit. med. J.*, **2**, 647.
Kniest, W. (1952). *Dtsch. med. Wschr.*, **77**, 676.
Komrower, G. M. (1951). *Brit. med. J.*, **2**, 1193.
Lehmann, J. (1946). *Lancet*, **1**, 15.
Lichtenstein, M. R. and Cannemeyer, W. (1953). *J. Amer. med. Ass.*, **152**, 606.
Medical Research Council (1950). *Ibid.*, **2**, 1073.
Muri, J. (1952). *Nord. Med.*, **47**, 155.
Nagley, M. M. and Logg, M. H. (1949). *Lancet*, **1**, 913.
Oppe, T. Personal Communication.
Sjoukes, P. (1952). *Ned. T. Geneesk.*, **96**, 2001.
Steel, S. J. (1952). *Brit. med. J.*, **1**, 415.
Swanson, J. N. (1949). *Lancet*, **2**, 175. Cited on p. 349 by O'Connor, J. A.
Tandhanand, S. and Buri, R. (1956). *Brit. med. J.*, **2**, 281.
Todd, R. McL. (1953). *Brit. med. J.*, **1**, 1247.
Warring, F. C. and Howlett, K. S. (1952). *Amer. Rev. Tuberc.*, **65**, 235.

THE DIAGNOSIS OF PERTUSSIS WITH SUPRALARYNGEAL AND MODIFIED PERNASAL SWABS

BY

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This paper analyses the results of diagnostic swabs taken from children seen at a pertussis contact clinic between December, 1950, and April, 1952.

Two new diagnostic techniques entailing contaminating swabs by cough, which were developed during this period, yielded a high percentage of positive cultures. A preliminary communication on one of these new techniques was published when the initial results of supralaryngeal swabs suggested their value (Bogdan, 1951c). The other technique, that of a modified pernasal swab used concurrently with a supralaryngeal swab, was developed in the course of this study and is described for the first time in this paper.

Method of Inquiry

Swabs were taken from the children, whose ages varied between 4 months and 9 years, whenever they attended the clinic, which was held three times a week. Much care was taken to ascertain the diagnosis, infectivity and stage of illness when swabs were taken.

Swabs were sent within three to five hours to the Department of Bacteriology of the Westminster Medical School where diamidine-penicillin-fluoride culture medium (Lacey, 1954) was routinely used. Negative cultures of swabs were reported to the clinic after 96 hours' incubation; positive cultures were not infrequently reported after 48 or 72 hours' incubation.

Method of Ascertaining Infectivity

Some children were free of symptoms and, though contacts, had actually escaped infection. Their swab cultures were negative and no carriers were detected. Some children already had a paroxysmal cough or were whooping. These continued to attend until they were symptom free. Some children were contacts with a brief but definite history of catarrhal symptoms and a mild persistent cough, which later became paroxysmal. They continued to attend the clinic until they lost all their symptoms. This prolonged observation enabled the observer to become certain on clinical grounds which children had pertussis and so acquire a reasonably reliable series of 'known' cases which are referred to below.

Some of the children were given suppressive treatment, as described previously, with chloramphenicol (Bogdan, 1951a and b) or with terramycin (Bogdan, 1952) after diagnostic swabs had been taken. Later swabs taken from these children are excluded from this survey. In view of waning infectivity, no swabs from untreated children taken later than the tenth day of the paroxysmal stage are considered for this survey.

In the circumstances every swab from each known case was considered capable of yielding a positive culture of *Haemophilus pertussis*, thus enabling the accuracy of each swab technique or combination of swab techniques to be assessed.

Method of Ascertaining Stage of Illness

Considerable care was taken in each case to ascertain how long each child had had symptoms such as nasal catarrh or a mild simple cough which, though persistent, only occurred occasionally, as if the throat were being cleared. This was taken as evidence of the pre-paroxysmal stage of the illness.

The onset of the paroxysmal stage was indicated when eventually the cough had changed in character and became paroxysmal and spasmodic, frequently terminating in a whoop and at times associated with vomiting at the end of each spasm.

Each type of cough was demonstrated for the mother's guidance to ensure that she understood the difference between a simple and a paroxysmal cough; it was thus possible to gather from the mother at what stage of the illness swabs were taken.

Preliminary Analysis: Pernasal and Postnasal Swabs

Pernasal swabs were taken in the manner described by Bradford and Slavin (1940), while postnasal

swabs were taken in the manner described by Cruickshank (1944).

The diagnostic accuracy obtained when pernasal and postnasal swabs were routinely used is seen from the swab culture results of 110 pairs of swabs from known cases of pertussis (Table 1).

TABLE 1
RESULTS OF PERNASAL AND POSTNASAL SWABS FROM KNOWN CASES OF PERTUSSIS

Technique	Incubation Period	Preparoxysmal Stage	Paroxysmal Stage (1-10)	Total
Total pairs taken	5	65	40	110
Per and/or post-nasal positive	4	53 (81%)	28 (70%)	85 (77%)
Pernasal positive	2	39 (60%)	22 (55%)	63 (57%)
Postnasal positive	3	44 (67%)	19 (57%)	66 (60%)
Both negative ..	1	12	12	25

In 77% (or 85/110) pairs one or both swabs were positive: 57% (or 63/110) of the pernasal swabs were positive: 60% (or 66/110) of the postnasal swabs were positive. In the preparoxysmal stage a higher proportion of positive cultures was obtained than after the onset of paroxysms, thus indicating the value of swab diagnosis at this important stage of the illness.

Supralaryngeal Swab Technique

The possibility of improving on these results led to the second part of this investigation and the development of the new supralaryngeal swab technique for the diagnosis of pertussis.

For supralaryngeal technique a normal straight swab is used with the mount made of either wood or wire, preferably the latter. The child is seated on the mother's knee so that it faces the doctor. The mother holds both the child's hands in one of her own and places the other firmly on its forehead, holding the child's head well back to enable the swab to be held directly above the lumen or upper end of the larynx (Fig. 1). The tongue is depressed by a broad spatula and the child is asked to cough. The direct positioning of the swab over the laryngeal outlet helps the doctor considerably in his attempt to obtain a freshly expectorated portion of mucus from the larynx. In order to obtain the mucus, correct positioning of the child and the swab is important.

If a child does not cough when asked, coughing can be provoked by touching the fauces or pharyngeal wall with the spatula, especially when the head is held well back which lessens the risk of vomiting. Towards the end of this trial, when more care was taken to ensure that a portion of mucus was adherent to each swab, results became increasingly positive.

An explanation to older children and parents that the procedure entails no more than 'coughing into a little stick' helped to inspire confidence and cooperation.

Absolute inability on the part of a child to cough, in spite of an attempt having been made with spatula and swab to provoke cough, provided reasonable evidence of insensitivity of the throat. This is most unlikely in pertussis, allowance being made for the early part of the incubation period. Thus this supralaryngeal technique may yield not only bacteriological evidence of pertussis, but provide clinical evidence against pertussis in some cases.

When an obvious portion of laryngeal mucus has been obtained on a supralaryngeal swab in catarrhal conditions other than pertussis, and symptomatic treatment with ephedrine-saline nasal drops and simple linctus had been begun, a negative culture report at 96 hours usually coincided with improvement in catarrh and cough. Quarantine of contacts in whom this was noticed was then curtailed. In no instance did subsequent events show that this course of action had been unjustified.

Supralaryngeal Results

During a period of 17 months 340 supralaryngeal swabs were taken from 174 known cases of pertussis. As with the series of pernasal and postnasal swabs described above, all these were taken before the eleventh day of the paroxysmal stage and before treatment. Of the entire series of supralaryngeal swabs, 65% (224/340) yielded positive cultures, 64 being positive in the first hundred, 51 in the second and 72 in the third. In the last 40 swabs only three

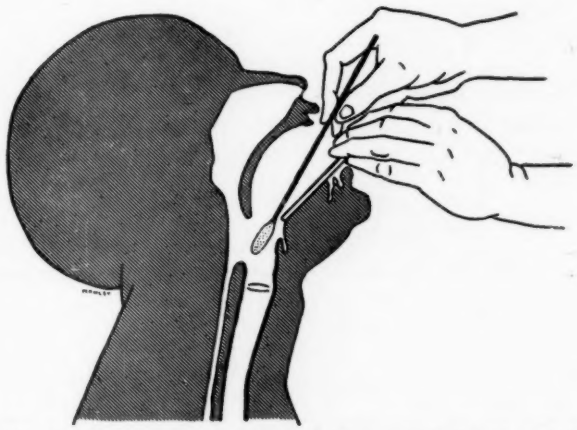

FIG. 1.—Position of head and swab when supralaryngeal swab is being contaminated by cough.

failed to yield a positive swab culture (Table 2), achieving a diagnostic accuracy of 92·5%.

TABLE 2

RESULTS OF 340 SUPRALARYNGEAL SWABS TAKEN FROM 174 CHILDREN WITH KNOWN PERTUSSIS

Number of Children	Number of Swabs	Single Suparlaryngeal Swab Cultures in Diamidine-penicillin-fluoride Medium	
		Positive	Negative
54	100	64	36
44	100	51	49
53	100	72	28
23	40	37 (92·5%)	3
174	340	224 (65%)	116

A new technical assistant helped to take the second hundred swabs. This may account for a temporary lessening in accuracy and subsequent improvement with experience in the third hundred cases. This prolonged trial of supralaryngeal swabs suggest that they are no less accurate than pernasal or postnasal swabs using diamidine-penicillin-fluoride selective medium cultures in all cases.

Comparison of Swab-Technique

To compare the results of supralaryngeal swabs with those obtained with pernasal and postnasal swabs an analysis was made of 109 known cases from whom three types of swabs were taken simultaneously.

The 'triple-swab' routine used at this stage of the investigations was as follows:

(1) A postnasal swab was taken first (from the nasopharynx behind the uvula).

(2) A short nasal swab was then passed into the nasopharynx and left there.

(3) A supralaryngeal swab was taken next, using a simple throat swab.

(4) The pernasal swab was then withdrawn.

The normal routine of taking pernasal swabs was modified to prolong the opportunity for each swab to become effectively contaminated in the nasopharynx. The likelihood of this having taken place was further increased by continued exposure of each pernasal swab to the cough provoked for the supralaryngeal swab. The actual swabs were modified in one further detail. A 4½ in. length of wire was used for taking pernasal swabs as this was found to be easier to introduce, less flexible and less likely to fall out.

By using this 'triple-swab' routine in taking swabs from known cases of pertussis, the diagnosis was confirmed bacteriologically in 92 (84%) of 109 cases (Table 3).

The postnasal swab alone confirmed the clinical diagnosis on 43% (47/109) occasions, supralaryngeal swabs on 55% (60/109) occasions and pernasal swabs (used in this modified way) on 72% (79/109) occasions.

Analysis of these results showed that the supralaryngeal and modified pernasal swab between them confirmed the diagnosis in 84% (92/109) of the known cases. The additional use of a third swab technique, a postnasal swab, had not increased the diagnostic accuracy of swabs in this series. This is noteworthy as further positives have usually been detected by each additional method employed whenever comparison has been previously made of diagnostic techniques used in pertussis.

The combination of a pernasal swab with a supralaryngeal swab therefore provides the best routine for obtaining positive cultures, when it is not possible to obtain a reasonable portion of fresh mucus on to a supralaryngeal swab.

Summary

Supralaryngeal swabs were taken from early known cases of pertussis. Positive culture reports from these swabs indicated an overall individual swab accuracy of 65% (224/340), attaining an accuracy of 92·5% at the end of the series. This technique is illustrated and described in detail.

A new modified pernasal swab technique to use with supralaryngeal swabs is described.

The new combination of a modified pernasal and a supralaryngeal swab had a diagnostic accuracy of 84% (92/109).

TABLE 3

TRIPLE-SWAB ROUTINE IN 109 KNOWN CASES OF PERTUSSIS

Stage of Illness	Children		Modified Pernasal Positive	Postnasal Positive	Supralaryngeal Positive
	Total	Positive			
Preparoxysmal	36	30	27 (75%)	17 (46%)	19 (53%)
Paroxysmal (1–10)	73	62	52 (71%)	30 (41%)	41 (56%)
Totals	109	92 (84%)	79 (72%)	47 (43%)	60 (55%)

Both new techniques depend on better contamination by cough of the swab. The importance of some laryngeal mucus adhering to supralaryngeal swabs is stressed.

All swabs were cultured on diamidine-penicillin-fluoride selective medium.

I am indebted to Dr. B. W. Lacey for the culture reports, to Dr. N. O. Richards under whose supervision the clinical work was done, to Dr. Charles F. Harris and Professor W. S. M. Craig for advice and encouragement, to Miss Anne Wigley and Miss Pamela Bennett of the British Red Cross Society for much skilled help assisted by Mrs. Hill; also to Miss Wendy Major for secretarial assistance and Miss Manley for the illustration.

The clinical part of this study was carried out with the aid of the Mary Scharlieb Research Studentship of the University of London at the Westminster Children's Hospital: the analysis of results in the Department of Paediatrics and Child Health, University of Leeds.

REFERENCES

Bogdan, A. (1951a). *Proc. roy. Soc. Med.*, **44**, 1065.
—— (1951b). *Lancet*, **1**, 764.
—— (1951c). *Ibid.*, **2**, 1204.
—— (1952). *Brit. med. J.*, **2**, 1186.
Bradford, W. L. and Slavin, B. (1940). *Proc. Soc. exp. Biol. (N.Y.)*, **43**, 590.
Cruickshank, R. (1944). *Lancet*, **1**, 176.
Kristensen, B. (1933). *J. Amer. Med. Ass.*, **101**, 204.
Lacey, B. W. (1954). *J. Hyg. (Lond.)*, **52**, 273.

THE SIGNIFICANCE OF THE C-REACTIVE PROTEIN ESTIMATION IN STREPTOCOCCAL AND ALLIED DISEASE

BY

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C-reactive protein is a specific protein which was first reported by Tillett and Francis in 1930 to be present in the serum of patients suffering from pneumococcal pneumonia. It was precipitated by the addition of the somatic C polysaccharide of the pneumococcus to the serum of these patients while in the acute phase of the illness, but the reaction disappeared during convalescence.

Originally thought to be a specific antibody against the pneumococcus, C-reactive protein was later found to appear in human serum in response to a variety of inflammatory conditions and to tissue necrosis. It is absent from normal serum. Abernethy and Avery (1941) suggested that it was associated with the albumin fraction of the serum after salt fractionation, but Perlman, Bullowa and Goodkind (1943) showed by electrophoretic analysis that C-reactive protein is an alpha globulin.

In contrast C polysaccharide antibody is found in the globulin portion of the serum after salt fractionation and has the electrophoretic mobility of gamma globulin, and does not disappear when the active phase of an illness has passed (Löfström, 1944). C-reactive protein was isolated and purified by MacLeod and Avery (1941). By injecting the purified protein into rabbits a specific antiserum was obtained which gave no reaction with normal human serum.

The protein has been further purified by crystallization, and the Schieffelin Company, New York, has produced the specific antiserum for C-reactive protein on a commercial scale. The use of this antiserum makes the detection of C-reactive protein in the serum a simple test.

Method

The test is a qualitative and quantitative precipitin reaction for C-reactive protein in a patient's serum.

The test was carried out in capillary tubes 90 mm. long and internal diameter 0·4 mm. A column, 3 cm. long, of C-reactive protein antiserum was drawn into the capillary tube and then a column of equal length of the patient's serum was drawn into the same capillary, care being taken to avoid air bubbles between the two sera. The tubes were placed vertically in stands (with antiserum in the upper part of the tubes), incubated for two hours at 37° C. and then left in the refrigerator for 22 hours.

Qualitative readings were obtained after two hours and expressed as positive or negative. Final readings were obtained after 24 hours and expressed quantitatively as the length of the column of precipitate in millimetres.

Cases Investigated

We were chiefly interested in the streptococcal diseases and those diseases probably allied to the streptococcal group.

One hundred and forty cases were studied and their distribution was as follows:

Primary tonsillitis	43 cases
Rheumatic fever	57 cases
Rheumatic chorea	7 cases
Nephritis	15 cases
Rheumatoid arthritis ..	5 cases
Schönlein Henoch purpura	9 cases
Erythema nodosum ..	4 cases

Multiple estimations were carried out in all cases, the tests being performed within 48 hours of admission to hospital and repeated at intervals of five to seven days.

Erythrocyte sedimentation rates (Westergren method) were estimated on blood samples taken simultaneously with those for the detection of C-reactive protein.

The sedimentation rates were expressed as millimetres in the first hour; below 10 mm. was regarded as normal, above 20 mm. as raised and from 10 mm. to 20 mm. as of doubtful significance.

Results and their Interpretation in the Different Groups

Primary Tonsillitis. In this group of 43 cases, two relapsed within a short interval of the initial infection. Haemolytic streptococci group A were

isolated from the throat swabs in 40% of the patients. Two-thirds of the remaining 60% had had oral penicillin or sulphonamides before admission to hospital and this probably explains why haemolytic streptococci were not grown from their throat swabs.

Positive C-reactive protein tests were obtained on the first to eighth days after the onset of symptoms and not later than the eighth day except in the two patients who had a relapse shortly after the initial infection. In these two cases positive results were obtained on the tenth and twelfth days respectively from the onset of the initial attack. It was also noted that the earlier treatment was begun the sooner the C-reactive protein test became negative, and the level of the C-reactive protein was roughly proportional to the severity of the infection with levels of 5 mm. in those patients who had an associated cervical adenitis. There was no significant difference in the results obtained in those patients from whom haemolytic streptococci group A had been isolated compared with those where the organism had not been found.

From the table it is not unreasonable to conclude that the C-reactive protein test correlates more closely with clinical activity than the E.S.R., which remained elevated for a few days after the C-reactive protein test had become negative in several cases.

Rheumatic Fever. This group of 57 cases was further subdivided as follows:

TWENTY-FOUR CASES WITHOUT CARDITIS. These included 14 cases where the patients attended with a history of limb pains following tonsillitis but had no objective signs of active rheumatism, five cases with no clinical activity on admission and five patients admitted with arthritis only, who never developed any signs of carditis.

THIRTY-THREE CASES WITH CARDITIS. The carditis was graded as mild in 12 patients who had minimal clinical signs as expressed by pulse rate and temperature, and only a soft localized apical systolic murmur which disappeared completely before discharge. In a further 21 patients the carditis was judged to be of a moderate to severe degree, since they had marked cardiac involvement. All these patients had an apical systolic murmur propagated to the axilla and many had a diastolic murmur; they had residual fading murmurs or other definite evidence of cardiac damage on discharge.

The 12 patients whose carditis was graded as mild were all treated with salicylates, while of the 21 patients who had a carditis of moderate to severe degree 15 were treated with salicylates and the remaining six with prednisolone.

CASES WITHOUT CARDITIS. In this subgroup of 24 cases the C-reactive protein test was negative unless the patients had an active arthritis at the time of or just before the test was done.

Of the 14 cases with limb pains only, nine were clinically inactive, with an E.S.R. under 10 mm., and a negative C-reactive protein test merely confirmed the inactivity. The other five patients had a sedimentation rate in the doubtful range which, together with a soft apical systolic murmur, made a decision difficult. The C-reactive protein test was negative and reflected the clinical view that there was no rheumatic activity and that the murmurs were functional.

The C-reactive protein test was negative in the five cases not clinically active on admission. Two of these cases had a raised E.S.R. between 30 and 40 mm. which settled to below 10 mm. within two weeks of admission without any other signs of clinical activity developing in the period before the E.S.R. fell to normal limits.

The five cases with arthritis were the only ones in which the C-reactive protein test was positive and it remained positive for a few days after the arthritis had subsided, becoming negative on an average by the fifteenth day of the disease.

CASES WITH CARDITIS. The C-reactive protein test was initially positive in all 33 cases of this subgroup and the length of time the test remained positive was proportional to the severity of the carditis. In the 12 cases where the carditis was graded as mild and treated with salicylates, the average time before the test became negative was 25 days. The average

TABLE 1

COMPARISON OF CLINICAL CONDITION, C-REACTIVE PROTEIN AND E.S.R. IN TONSILLITIS

No. of Cases	Clinical State	C-reactive Protein	E.S.R.		
			Normal	Doubtful	Raised
28	Active	Positive, 1 to 6 mm., in all cases	2	7	19
3	Subsiding	Negative 2 cases. Positive 1 case, 1 mm.		2	1
12	Convalescent	Negative all cases	6	3	3

C.R.P. = C-reactive protein.

time the test took to become negative from the onset of symptoms was longer in the patients whose carditis was graded from moderate to severe; it was 80 days in the 15 cases treated with salicylates but only 35 days in the six cases treated with prednisolone as shown in Fig. 1.

Correlation of Clinical Signs with C-reactive Protein in Rheumatic Fever. The C-reactive protein test remained positive after the patients became afebrile and the arthritis had subsided, and became negative about the time the tachycardia was settling and the murmurs started to fade.

The test gives a definite positive or negative result whereas the point where the pulse is settling and the murmurs disappearing is more easily seen from the records in retrospect than at the actual time.

Clinically in a few severe cases there was doubt as to the clinical activity for about a week after the C-reactive protein test had become negative. In those cases which relapsed the C-reactive protein test became positive a few days before the relapse became clinically apparent.

Comparison of E.S.R. and C-reactive Protein in Rheumatic Fever. The E.S.R. followed the general trend of the C-reactive protein but appeared to lag behind in returning to normal as can be seen in Fig. 1. This is further illustrated by the results in the five cases which were inactive on admission and had a negative C-reactive protein test, since in two of these cases the E.S.R. was raised at 30 to 40 mm. and took two weeks to subside to within normal limits.

The E.S.R. also showed a delay in rising and therefore did not foreshadow the clinical recurrences as did the C-reactive protein. This delay occurred in all grades of carditis and Fig. 2 illustrates it in a case of mild carditis.

In one patient the E.S.R. was particularly misleading since it remained below 10 mm. for the whole course of the disease, although there was undoubted clinical activity. The C-reactive protein gave a more accurate index of this activity (Fig. 3).

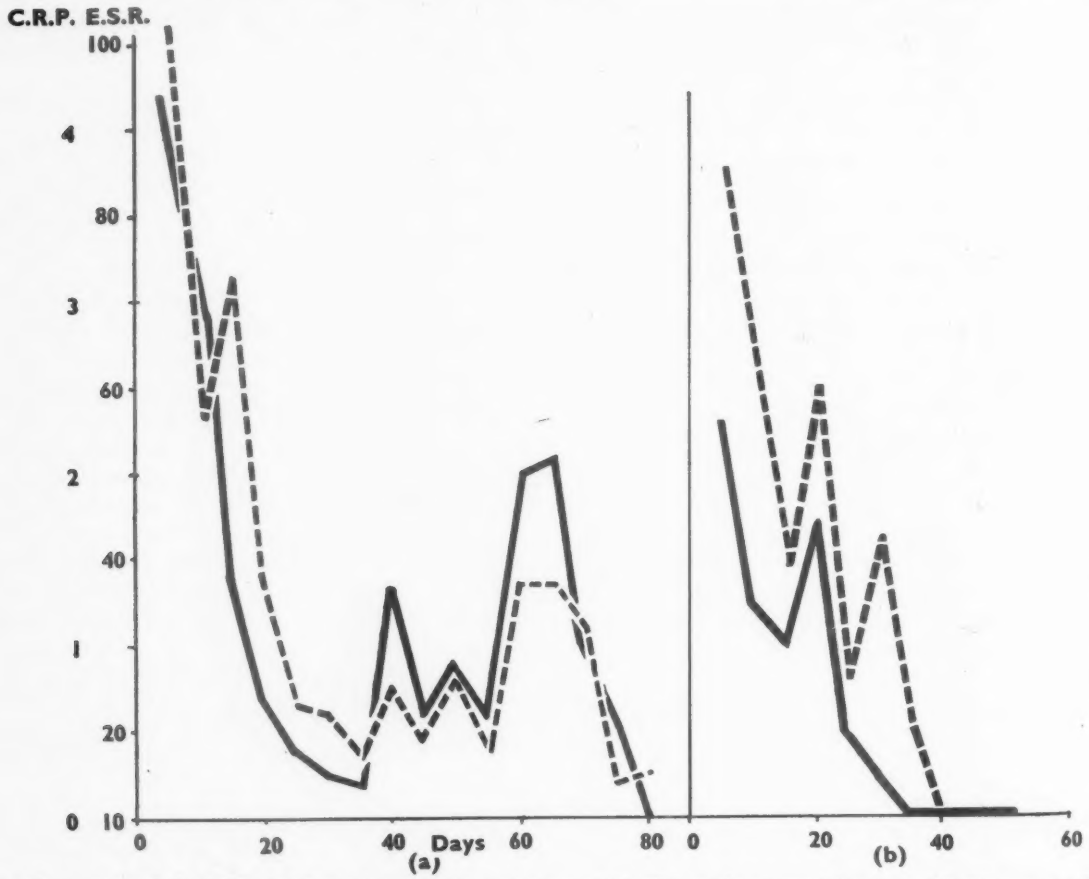

FIG. 1.—Comparison of the E.S.R. and C-reactive protein in moderate carditis. The graphs represent the mean of the 15 cases on salicylate (*a*) and the six on prednisolone (*b*). C.R.P. .————. mm. of precipitate. E.S.R. – – – – mm. Westergren. Note that 10 mm. on the E.S.R. scale is placed level with the absence of a C-reactive protein deposit.

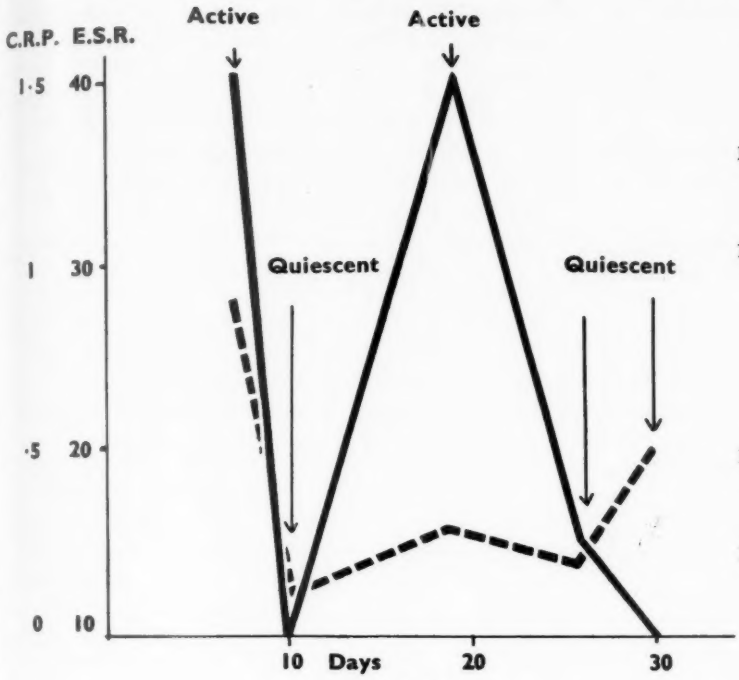

FIG. 2.—Lag of E.S.R. behind C-reactive protein in clinical recurrence of mild carditis (Case 22).

C.R.P. .————. mm. of precipitate.
E.S.R. – – – – mm. Westergren.

Note that 10 mm. on the E.S.R. scale is placed level with the absence of a C.R.P. deposit.

FIG. 3.—Normal E.S.R. and positive C-reactive protein in carditis and tonsillitis (Case 30).

C.R.P. .————. mm. of precipitate.
E.S.R. – – – – mm. Westergren.

Note that 10 mm. on the E.S.R. scale is placed level with the absence of a C.R.P. deposit.

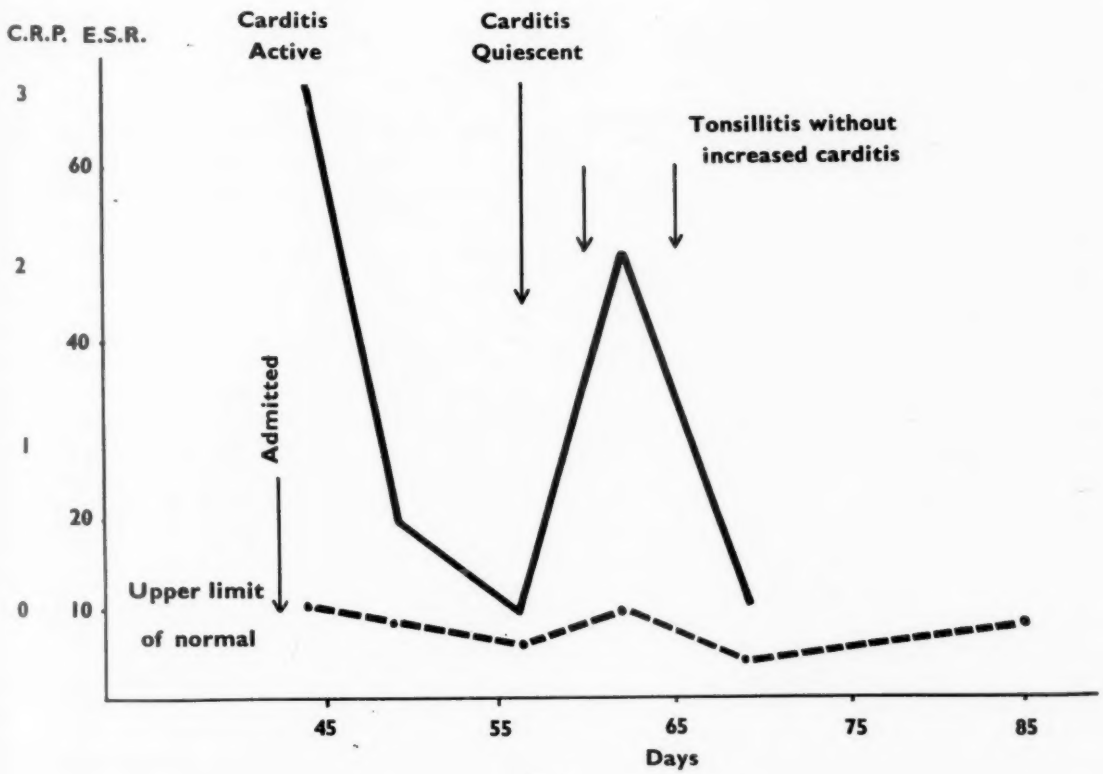

FIG. 3.

Comparison of C-reactive Protein in Tonsillitis and Rheumatic Fever. In primary tonsillitis, C-reactive protein was not present after the eighth day unless there was a recurrence of the tonsillitis. Fig. 4 shows the results of the C-reactive protein test in the one case of tonsillitis which was followed by rheumatic fever contrasted with an uncomplicated case of tonsillitis. When the child was clinically well the C-reactive protein level actually rose before there was clinical evidence of carditis and persisted throughout the course of the carditis.

Six patients developed tonsillitis during the course of the rheumatic fever attack. In four, the tonsillitis was not complicated by any recurrence of carditis and the C-reactive protein test became negative between the sixth and the eighth day. In the remaining two patients the carditis recurred and the C-reactive protein persisted until the condition subsided on the 24th and 25th day respectively after the onset of tonsillitis.

The results in these patients suggest that if the C-reactive protein test does not become negative within eight days, then a recurrence of the carditis should be anticipated.

Rheumatic Chorea. Seven children aged 6 to 14 years with active chorea but no carditis had E.S.R.s ranging from 8 to 18 mm.; the C-reactive protein test was negative in all cases.

One case with mitral stenosis due to a previous carditis later developed a mild exacerbation (with rise in pulse rate, increase in cardiac murmurs and recurrent epistaxis) as the chorea was subsiding. The E.S.R. rose from 4 to 18 mm. the C-reactive protein test became positive (1·5 mm.) and there was still a trace of the protein three weeks later when the sedimentation rate was 10 mm. and the chorea had subsided.

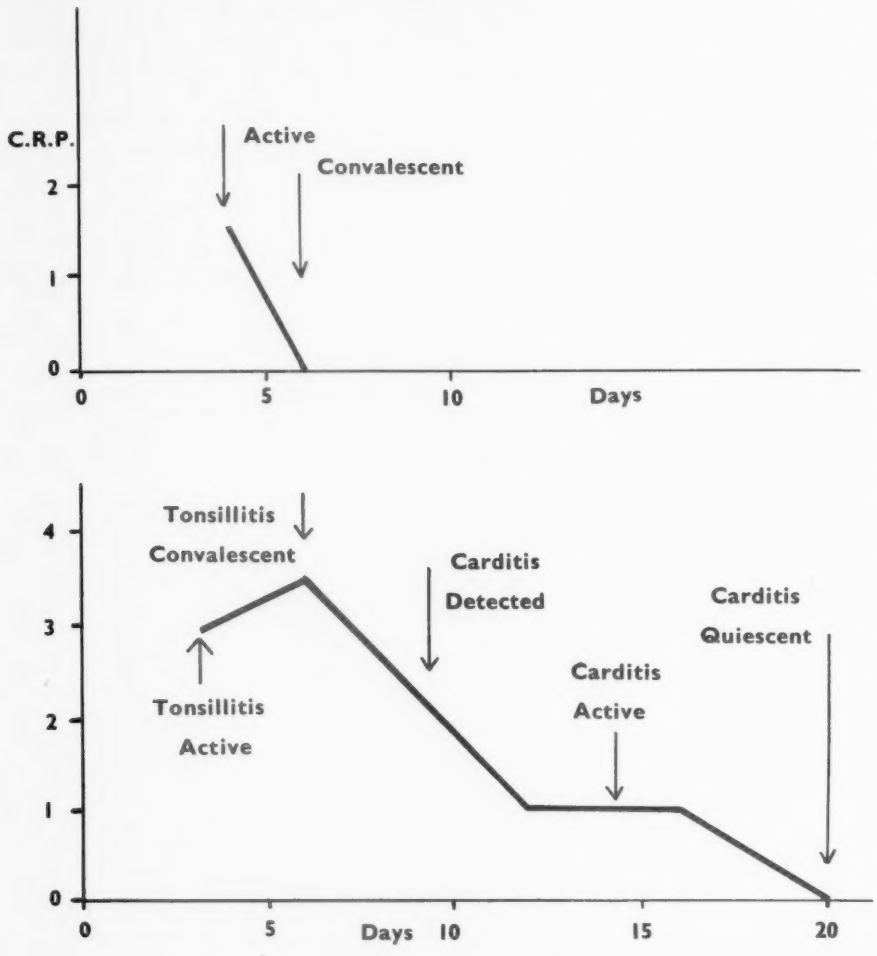

FIG. 4.—Graphs (top) of a case of uncomplicated tonsillitis (Case 41) and (below) of tonsillitis complicated by rheumatic fever and mild carditis (Case 20).
C.R.P. .————. mm. of precipitate. E.S.R. – – – – mm. Westergren.
Note that 10 mm. on the E.S.R. scale is placed level with the absence of a C.R.P. deposit.

Nephritis. There were 15 cases in this group. All gave a history of tonsillitis or upper respiratory tract infection one to five weeks before the onset of the nephritic symptoms. These infections had not been treated or the patients had received inadequate doses of oral penicillin or sulphonamides.

The common findings on examination of the urine were albuminuria, microscopic haematuria and granular casts. All the patients had a considerably raised sedimentation rate and the majority had hypertension and a raised blood urea level.

Seven of the 15 cases had a positive C-reactive protein test on admission. Six of these seven cases were febrile and had active throat infections whereas only one of the eight cases in the negative C-reactive protein

group had clinical evidence of a throat infection. Otherwise there were no significant differences between the two groups in regard to clinical severity or time the E.S.R. took to return to normal values.

No positive C-reactive protein result was recorded after the eighth day, and negative results were recorded as early as the fourth day after the onset of nephritic symptoms. The sedimentation rate took an average of 25 days to settle below 20 mm. The average time for the haematuria and albuminuria to decrease was 16 days and that for the urine to become normal on microscopy was 40 days.

The C-reactive protein is not as reliable a guide to the activity of nephritis as the E.S.R. seems to be.

The tissue reaction as judged by the presence of C-reactive protein differs in acute nephritis from that in rheumatic fever, because in the latter it persists throughout the active course of the disease.

Rheumatoid Arthritis. In all five cases the C-reactive protein remained elevated for long periods (up to two months in three cases). The rise in the C-reactive protein preceded the rise in the E.S.R. and the appearance of clinical joint manifestations and often became negative before the E.S.R. fell to normal.

Schönlein Henoch Purpura. There were nine patients in this group. The C-reactive protein test was negative in six cases and positive in the remaining three (0·5 to 2·5 mm. on the second to ninth day of disease with E.S.R.s below 15 mm.). The test became positive in one of two cases which relapsed. The cases with a positive result all had arthritis at the time of the test, whereas those with a negative test had purpuric manifestations only.

Two cases also had renal involvement; one had a persistently negative test although the E.S.R. became elevated with the onset of the nephritis (test taken on the second day of albuminuria and at weekly intervals thereafter); the other had arthritis and the positive test was more likely to have been associated with the arthritis than with the nephritis.

Erythema Nodosum. In only four of these cases could the rash be definitely related to a streptococcal infection and in these a positive C-reactive protein test was recorded as late as the 20th day after the appearance of the rash. The E.S.R. again lagged behind the C-reactive protein in returning to normal and remained raised even when there was no evidence of activity.

Discussion

Apart from two British papers by Hill (1951, 1952) all the investigations on C-reactive protein have been carried out in Scandinavia and America. Some of the literature was reviewed in editorials of the *Lancet* (1954) and the *British Medical Journal* (1956).

In this series the results in uncomplicated tonsillitis show quite clearly that the C-reactive protein soon disappears from the serum. In treated cases a positive result was not obtained after the eighth day of disease. A persistently positive test should make one suspect the development of a complication of the streptococcal infection such as rheumatic fever. This was clearly shown in Case 20 (Fig. 4) where, although the tonsillitis subsided, C-reactive protein persisted in the latent interval before carditis was detected.

Anderson and McCarty (1950) found that in the majority of patients with streptococcal infection followed by rheumatic fever, C-reactive protein is present during the interval between the subsidence of the infection and the onset of carditis. Therefore they concluded that this latent interval is usually a period of subclinical rheumatism.

In the majority of results published on rheumatic fever a rough correlation has been noted between the C-reactive protein results and the E.S.R. During early convalescence it has been noted that there is a tendency for the sedimentation rate to remain raised after the C-reactive protein has disappeared; similar results are reported in this series. In one patient Case 30 (Fig. 3) in this series of 57 cases of rheumatic fever, the combination of a normal E.S.R. with a positive C-reactive protein occurred. This occasional, but nevertheless very important discrepancy between the E.S.R. and the C-reactive protein has also been observed by Anderson and McCarty (1950). It points to the great value of the C-reactive protein as an index of rheumatic activity.

In our seven cases of chorea, six were uncomplicated by carditis and had negative C-reactive protein results. Anderson and McCarty (1950) and Stollerman, Glick, Patel, Hirschfeld and Rusoff (1953) likewise noted the absence of C-reactive protein in cases of uncomplicated Sydenham's chorea. The seventh case had a negative result until carditis developed as the chorea was subsiding, then the protein appeared in the serum and persisted throughout the carditis.

The five children with acute rheumatoid arthritis in this study all gave a positive C-reactive protein test, frequently for long periods, both in the presence of clinical activity and also in the absence of overt joint manifestation. Other studies of the C-reactive

protein in rheumatoid arthritis have been in adults (the largest series by Hill, 1951), but since the clinical picture of acute rheumatoid arthritis in children differs from that in adults the results are not strictly comparable.

The reaction of the tissues in other diseases which may follow streptococcal infection has been mentioned only by Adams (1956). and seven cases of acute glomerulonephritis were included in his series of 'rheumatic fever, rheumatoid arthritis and streptococcosis'. Of the seven cases three had a positive and four a negative C-reactive protein test at the onset of the disease but no follow-up tests were carried out.

In the present series the results indicate that a positive C-reactive protein test in early glomerular nephritis is due to the associated streptococcal infection and not to the renal involvement, since the test became negative rapidly after the infection cleared.

In Schönlein Henoch purpura a positive C-reactive protein test was associated only with an acute arthritis. The uniformly positive results of the C-reactive protein test in active rheumatic carditis and the uniformly negative results in nephritis after the subsidence of the streptococcal infection are possibly due to a different tissue response.

Summary

The C-reactive protein was compared with the erythrocyte sedimentation rate and the clinical state in 140 cases of streptococcal and allied diseases.

The C-reactive protein estimation is an easy test to perform. Unlike the E.S.R. it is not influenced by other factors, such as anaemia or alterations in serum protein fractions, nor has it any range of doubtful values but gives a definite positive or negative result. Although it is a non-specific test which cannot be used for diagnosis, it has a definite value in assessing the degree of activity, particularly in rheumatic fever and rheumatoid arthritis. In these diseases there is closer correlation of the clinical activity with C-reactive protein than with the E.S.R. In acute nephritis it is of value only in assessing the persistence of streptococcal infection, but not in assessing the nephritic state.

I should like to thank Dr. A. Holzel and Dr. W. H. Patterson, under whose direction this study was carried out, for their advice and encouragement and Dr. L. Parker for his advice and the bacteriological investigations.

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References

Abernethy, T. J. and Avery, O. T. (1941). *J. exp. Med.*, 73, 173.
Adams, F. H. (1956). *J. Pediat.*, 49, 16.
Anderson, H. C. and McCarty, M. (1950). *Amer. J. Med.*, 8, 445.
Editorial (1956). *Brit. med. J.*, 2, 145.
—— (1954). *Lancet*, 1, 350.
Hill, A. G. S. (1951). *Ibid.*, 2, 807.
—— (1952). *Ibid.*, 2, 558.
Löfström, G. (1944). *Brit. J. exp. Path.*, 25, 21.
MacLeod, C. M. and Avery, O. T. (1941). *J. exp. Med.*, 73, 183.
Perlman, E., Bullowa, J. G. and Goodkind, R. (1943). *Ibid.*, 77, 97.
Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I. and Rusoff, J. H. (1953). *Amer. J. Med.*, 15, 645.
Tillett, W. S. and Francis, T. Jr. (1930). *J. exp. Med.*, 52, 561.

CEREBRAL ABSCESS AS A COMPLICATION OF NEONATAL SEPSIS

BY

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(RECEIVED FOR PUBLICATION APRIL 16, 1957)

Our reason for reporting two cases of cerebral abscess secondary to neonatal sepsis is the apparent rarity with which this complication occurs when the relatively high incidence of infection in the newborn period is considered. Crosse and Macintosh (1953) found that 10% of babies delivered at home and 14% of those delivered in hospital developed infections in the first 10 days of life; yet only four examples of this complication appear to have been described so far. The only reported survival was described by Farley (1949) in a baby whose illness began with a small boil on the face. This was followed by thrombophlebitis, cavernous sinus thrombosis and eventually a very large abscess in the left frontal lobe. Johnson, Elmore and Adams (1953) reported three cases, all of which died and in all of which a maternal respiratory infection was thought to be the source of infection.

Holt (1898) reviewed 32 cases of cerebral abscess in children, five of whom were under the age of 5 months, but in none of these was the infection connected with neonatal sepsis. One of Sandford's two cases (1928) was probably an example, although he did not claim it as such. Since attention has focused on neonatal sepsis only relatively recently, it may well be that its association with the development of severe infections in later months has not been recognized in the past.

Case Reports

Case 1. Jacqueline E., an 8-week-old infant, was admitted in April, 1956, with failure to thrive. She had vomited intermittently from birth and her weight gain had averaged less than 2 oz. per week.

Both the pregnancy and labour were normal and she was born at home weighing 7 lb. 12 oz. There was difficulty in feeding her until the third day, when she vomited some reddish-black material. However, melaena was absent and breast feeding was soon satisfactorily established. Septic spots appeared on the left side of the face during the first few days and at the end of the first week; the left thumb became red and swollen; she became ill and lost 1 lb. in weight. The thumb was incised by the general practitioner and a course of intramuscular penicillin was prescribed. She appeared to make a good recovery but at the age of 3 weeks she again became acutely ill with vomiting, fever and weight loss, necessitating admission to a local hospital. There she was found to have an erysipeloid eruption of the left thigh which responded to further intramuscular penicillin. However, pyrexia recurred with looseness of the stools, and her general condition again deteriorated and she became dehydrated. Improvement began after a course of tetracycline, but the baby was taken home against medical advice. Her progress at home was not satisfactory; feeding was difficult and weight gain was exceedingly slow. Inevitably, experiments were made in varying the type and quantity of the feeds without benefit. She was admitted to The Hospital for Sick Children (under the care of Dr. Wilfrid Sheldon), as vomiting had recurred for the previous five days and her general condition was deteriorating. She had had no fits or focal neurological symptoms at any time before admission.

The father, mother and three siblings were healthy, but the mother had suffered from a febrile upper respiratory tract infection at the time of the present infant's delivery and a sibling developed acute tonsillitis a few days later.

On admission the child looked pale and ill; the temperature was 102° F., the pulse 138 per minute and the respirations 30 per minute. The cry was vigorous and not high-pitched. The anterior fontanelle was tense, though not bulging, and the skull circumference was 14½ in. There was no nuchal rigidity, and the limbs were hypotonic. The retinal veins were full but there were no retinal haemorrhages and papilloedema was absent. There was no sign of any primary septic lesion. The liver and spleen were not enlarged and there were no skin haemorrhages.

A catheter specimen of urine was normal. The haemoglobin was 53% (7·84 g.) per 100 ml. and the total leucocytes 16,400 per c.mm. (neutrophils 73%; lymphocytes 27%). Electrophoresis of serum protein showed no deficiency of gamma globulin.

A subdural haematoma was suspected and bilateral subdural taps were therefore attempted on the day of admission. Whilst no fluid collection was encountered on the right side, the left side yielded 60 ml. of thick

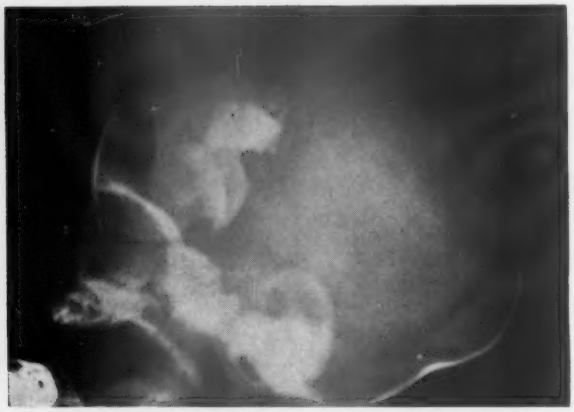

FIG. 1.—Skull plate of Case 1 showing the abscess cavity outlined by thorotrast and air.

yellow pus from which non-haemolytic streptococci were readily cultured. This organism was sensitive to all antibiotics. Intramuscular penicillin was given initially and was followed by a course of chloramphenicol for the first week. The following day a further 60 ml. of pus were aspirated, which again yielded the same organism. A blood transfusion was given which raised the haemoglobin level to 96% (14·21 g.) per 100 ml. Aspiration on the third day yielded 25 ml. of pus, now noticeably thinner. Plain radiographs of the skull showed only slight widening of the sutures. The baby was then transferred to the Neurosurgical Department under the care of Mr. Wylie McKissock. After radiographs following air replacement of the pus the extent of the cavity suggested that the abscess lay in the left frontal lobe rather than in the subdural space. This was confirmed the following day by outlining the cavity with thorotrast and air (Fig. 1).

Repeated aspiration was carried out with instillation of 10,000 units of crystalline pencillin and 50 mg. streptomycin. Gradually the quantity of pus diminished and it became less viscous. After 19 days' treatment no organisms could be seen in the stained smear and culture was sterile. The relatively long time needed to achieve this result was thought to be due to the formation of loculi in the abscess cavity, which led to the recovery of thin fluid or thick pus depending on which part of the cavity was aspirated. The temperature had remained normal since the fifth day and progress with regard to feeding had been equally satisfactory; the weight gain exceeded an average of 1 oz. per day. By the 27th day the abscess cavity had shrunk considerably (Fig. 2), but further aspiration produced no improvement. Therefore, on the 36th day, a left frontal lobectomy was carried out under general anaesthesia by one of us (K.W.E.P.). The frontal lobe was firm due to gliosis and, after removal, section of the frontal lobe showed that the specimen consisted of abscess cavity surrounded by gliosed brain, very little normal brain tissue having been removed.

The immediate post-operative period was complicated by a series of focal fits involving the right hand on the evening after operation. The fits were eventually controlled by phenobarbitone and the only neurological sequel was a mild right hemiparesis, which three weeks later was barely noticeable. Pyrexia of 100 to 101° F., associated with collapse of the left lower lobe of the lung, occurred on the evening of the second post-operative day and resolved on the fifth day. Progress was thereafter uneventful; the baby remained afebrile and took feeds without vomiting.

On discharge, three weeks after operation, her general condition was excellent, the frontal wound was healed and the fontanelle was soft. A minimal right hemiparesis was still present.

She was re-admitted two weeks later as the mother had noticed that the fontanelle was bulging for the previous 24 hours. Radiography after aspiration of fluid from the left frontal cavity and air replacement revealed a subdural collection of fluid on the left side covering the whole hemisphere and communicating with the ventricular system by an opening in the left frontal horn. On July 25 a left parietal craniotomy was performed when the fluid was evacuated and the subdural membranes removed. The subdural space was obliterated by allowing the dura to collapse from the skull on to the underlying hemisphere. The child's immediate recovery was satisfactory but she died suddenly that same evening. A necropsy failed to reveal the immediate cause of death nor did it reveal any obstruction of the C.S.F. pathways as a cause of the subdural collection of fluid.

Case 2. John L. was admitted on May 21, 1953, at the age of 19 days having had convulsions for two days.

The pregnancy and labour were both normal, and the baby's birth weight was 8 lb. 2 oz. The condition was satisfactory until the fourth day when a boil appeared on the right side of the head. This was incised releasing pus and gradually disappeared, but by the 17th day a swelling was noticed over the skull in the right posterior parietal region. The following day convulsive movements began in the left leg and became generalized. Lumbar puncture at a local hospital yielded cloudy cerebrospinal fluid under normal pressure. This con-

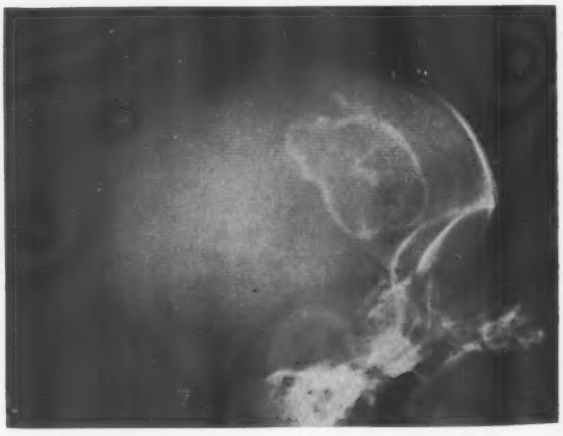

FIG. 2.—Skull plate of Case 1 showing the extent of the abscess cavity after four weeks' treatment.

tained 1,400 leucocytes per c.mm. (neutrophils 52%, monocytes 48%), 180 mg. protein per 100 ml. and 45 mg. sugar per 100 ml. with no organisms on stained film or culture.

On transfer to the Neurosurgical Department at The Hospital for Sick Children, Great Ormond Street, his general condition was good. The anterior fontanelle tension was normal and there was no head retraction. A small scab marked the site of the healed pustule in the right parietal region where a soft fluctuant swelling, 3 cm. in diameter, was palpable. The overlying skin was normal but the bone at the periphery of the swelling appeared to be elevated. Spontaneous movements were diminished in the left arm and leg, which were hypertonic with increased tendon reflexes.

FIG. 3.—Radiograph of tibia of Case 2, showing osteomyelitis.

Radiographs of the skull showed periosteal elevation with underlying osteoporosis at the site of the swelling. Ventriculography performed on the day of admission showed slight displacement of the third ventricle to the left and depression of the roof of the posterior part of the right lateral ventricle, the appearances being consistent with a right tempero-parietal space-occupying lesion. Craniotomy was performed on the same day when thick pus was released from a sub-periosteal abscess; removal of the infected part of the calvarium revealed an underlying extradural abscess with an intracerebral extension. Catheters were inserted into the extradural space and four-hourly instillations of penicillin begun.

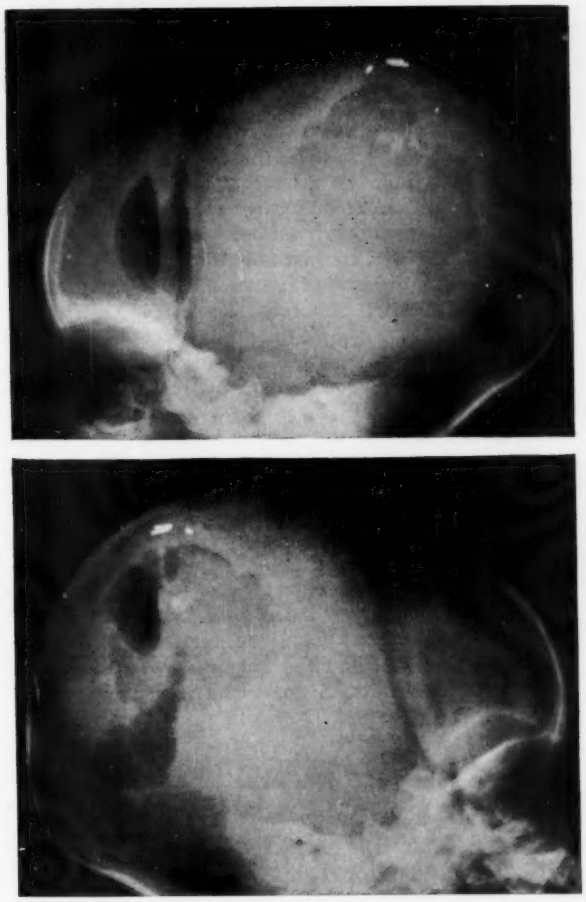

FIG. 4.—Ventriculograms of Case 2 showing a large cavity in the right parietal region, dilatation of the anterior horns of the lateral ventricles, and the intercommunication. A large area of osteomyelitis of the skull can also be seen.

The organism isolated from the pus proved to be a coagulase-positive staphylococcus, sensitive to penicillin and streptomycin both of which were given intramuscularly in large doses. The baby's general condition improved and the frequency of the convulsions diminished. On the 28th day of life, however, an area

of cellulitis appeared in the left leg where intravenous fluids had been given, and a week later an abscess had localized, from which a coagulase-positive staphylococcus was again isolated. The dosage of penicillin was increased to 1 million units four-hourly and the streptomycin was changed to 0·25 g. four-hourly of sulphafurazole to which the organism was also sensitive *in vitro*. However, this infection subsequently progressed to frank osteomyelitis of the tibia (Fig. 3).

The scalp wound healed satisfactorily, but a radiograph of the skull taken on the 34th day of life showed extensive bone erosion characteristic of osteomyelitis. A second operation was performed five days later when the affected bone was rongeured away and sequestra were removed. Daily lumbar punctures were done to reduce brain herniation, and, although the cerebrospinal fluid was sterile, it still contained an excess of leucocytes and protein. For the next three weeks the infant vomited at intervals and did not gain weight. The left arm and leg remained spastic.

On the 64th day of life, the convulsions began again and ventriculography was repeated. Symmetrical dilatation of the anterior horns of the lateral ventricles was demonstrated and air was shown to pass into a cavity in the right parietal region which communicated freely with the right lateral ventricle (Fig. 4). The baby's general condition gradually deteriorated after this; staphylococci appeared in the ventricular fluid and spinal fluid, and he died on August 4, 1953, aged 13 weeks and 5 days.

Dr. Martin Bodian at necropsy confirmed the presence of a large cerebral abscess in the right parietal lobe which had ruptured into the ventricle. There was also osteomyelitis of the skull and the left tibia. Toxic changes were present in the liver, heart and kidneys, as was a terminal pulmonary oedema.

Discussion

Spread of infection to the brain follows well-recognized routes. Thus Case 2 is an example of direct spread from local osteomyelitis. From septic lesions of the face the infection may reach the brain via the emissary veins and the cavernous sinus (Farley, 1949). A blood-borne infection may also be responsible, recorded primary lesions including paronychia, pneumonia and umbilical sepsis. Agammaglobulinaemia is a rare cause of widespread neonatal infection, but the gamma globulin estimation done in our Case 1 was normal. An interesting association is the occurrence of cerebral abscess after splenectomy (Johnson *et al.*, 1953). Although this was ascribed to infection of an intracerebral haematoma due to thrombocytopenic purpura, an increased liability to infection has been thought to follow splenectomy (Gofstein and Gellis, 1956). The susceptibility of the newborn is such as to render them liable to infection by organisms commonly regarded as non-pathogenic. Johnson *et al.* (1953), who stressed the danger of maternal infection at the time of birth, advocated immediate prophylactic treatment with antibiotics. Although the mother of Case 1 was not treated with an antibiotic, the infant was given intramuscular penicillin relatively early for a minor infection. Moreover, the responsible organism was a non-haemolytic streptococcus which, even if it had been isolated from the mother, would not have excited attention.

To add to the obvious difficulty of neurological localization at this age, the classical signs of raised intracranial pressure may be minimal or absent. Even if present, the causes of vomiting in infancy are protean and convulsions may be the non-specific response to fever of any cause. In neither of our cases was the heart rate slowed. Although any of the commonly described neurological manifestations of cerebral abscess can be present the only definite sign that may be encountered in infancy is a full anterior fontanelle. This raises the question of differential diagnosis from meningitis and other space-occupying lesions, particularly subdural haematoma, both of which are the more common conditions, and we admit that the clinical diagnosis may be extremely difficult. Subdural haematoma, which not infrequently produces a febrile systemic response, can only be exluded by a subdural tap. Meningitis usually gives rise to a more acute clinical picture with meningeal irritation, although the latter may be misleadingly absent. In our limited experience, we feel that cerebral abscess should be considered a possible diagnosis in any infant with a full anterior fontanelle, who has become gradually but increasingly ill following infection elsewhere in the body.

Once a cerebral abscess is suspected, localization may be possible on careful clinical examination; the abscess should then be aspirated and its extent determined radiologically after replacement with air or radio-opaque medium. Frequent aspiration and instillation of the appropriate antibiotic should be continued until the cavity begins to obliterate. In the case described by Farley (1949) no other operative measure was required and the cavity closed spontaneously after six months. In our Case 1, the cavity could not be reduced to less than 2 cm. in size and for this reason, excision, amounting to a frontal lobectomy, was necessary.

When no evidence of localization is forthcoming, little further help can be expected from plain radiographs of the skull unless gas-forming organisms are present. Arteriography is the theoretical investigation of choice but is technically impracticable at this age. Similarly, the limitations of electro-encephalography in infancy detract from its

usefulness in the localization of a suspected abscess. Lumbar puncture is often performed to exclude meningitis but is not without danger from prolapse of the cerebellum into the foramen magnum, although the flexibility of the sutures will preclude coning of the supratentorial structures. Ventriculography carries the risk of intraventricular rupture of the abscess, but this investigation, preceded by exploration of the subdural space, may be essential for localization. The abscess should then be aspirated immediately after ventriculography.

With regard to the prognosis, Farley's patient is the only one among those we have reviewed to have survived, and was well when demonstrated at the Royal Society of Medicine at the age of 6 years. Convulsions occurred during the first year and speech was retarded until the age of 4, but the eventual mental development was normal (Farley, 1952). Subsequently, this child's fits recurred and a slight hemiparesis became detectable (Farley, 1957).

Our first patient, who had made a good recovery after a frontal lobectomy, died suddenly after a second operation for an accumulation of subdural fluid. This unusual complication should not be a contra-indication to excision of a residual abscess as the final stage of treatment in similar cases.

Summary

Two cases of cerebral abscess complicating neonatal sepsis are described. In one of these, a maternal infection was present at the time of birth. The diagnosis and treatment of the condition is discussed and the literature of cerebral abscess in the neonatal period is briefly reviewed.

We are indebted to Dr. Wilfred Sheldon and Mr. Wylie McKissock for permission to publish these cases, to Dr. Martin Bodian for the post-mortem findings in Case 2 and to Mr. Derek Martin for the illustrations.

References

Crosse, V. M. and Mackintosh, J. H. (1953). *Brit. med. J.*, **1**, 1374.
Farley, D. L. B. (1949). *Lancet*, **1**, 264.
—— (1952). *Proc. roy. Soc. Med.*, **45**, 400.
—— (1957). Personal communication.
Gofstein, R. and Gellis, S. S. (1956). *A.M.A. J. Dis. Child.*, **91**, 566.
Holt, L. E. (1898). *Arch. Pediat.*, **15**, 81.
Johnson, G. D., Elmore, S. E. and Adams, F. F. (1953). *J.S.C. med. Ass.*, **49**, 281.
Sanford, H. N. (1928). *Amer. J. Dis. Child.*, **35**, 256.

HYDATID CYST OF THE KIDNEY IN A CHILD

BY

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The incidence of hydatid disease varies considerably in different parts of the world. It is common in South America, Australia and parts of Asia; for example, in Beirut, Syria, 0·75% of hospital admissions over a 10-year period were patients with echinococcus cysts (Baurys, 1952). In Great Britain there are no figures of value about the incidence of hydatid disease because there is no proper system of reporting primary cases infested here as distinct from those infested overseas. The total primary cases are probably fewer than 50 per year, of which nearly half are patients who become infested in endemic areas in other countries (Bensted, 1957). The only endemic area in Great Britain is South Wales; the disease is five times commoner in Wales than in England (Mackay, 1956). Wolfe (1943) reviewed 34 cases, which had occurred over a period of 12 years, from the hospital reports of the Royal Infirmary, Cardiff.

The disease is rarely seen after the fourth decade of life and about 26·2% of hydatid cysts occur in patients under 15 years of age. The organic distribution of cysts in children is liver 76·2%, lung 11·1%, brain 4·3% and kidney 1·2% (Dew, 1928). Gray (1953) reviewed the cases of hydatid disease found in the children of Cardiff and did not mention a cyst in the kidney. This confirms the impression drawn from Bensted's and Dew's figures that renal hydatid cyst in a child in Great Britain is a very rare disease.

Case Report

Philip C, aged 7 years, was sent to the Duchess of York Hospital because at a routine school examination he was found to have an enlarged liver. He had no complaints and was leading a normal, active life at school. His bowels, micturition, sleep, appetite and weight were all satisfactory. He had lived in Stockport, an industrial town, all his life, apart from one holiday at the seaside in North Wales. In 1953 the family kept a puppy for one year but no evidence was obtained to suggest that the puppy was the source of infection.

In 1952 the child was admitted to hospital with a pyrexia of unknown origin, possibly glandular fever or benign lymphocytosis. The abnormal physical signs were a low-grade pyrexia and an enlarged liver. On admission the total white cell count was 45,000/c.mm. (lymphocytes 80%, polymorphs 20%). A Paul Bunnell test was positive at 1:64 and two weeks later it was positive at 1:4. A month after admission the child was well, the pyrexia had subsided and the liver was not palpable. The total white cell count was then 13,400/c.mm (polymorphs 47%, lymphocytes 41%, eosinophils 10%, monocytes 2%). No cause was found for the high eosinophil count at the time.

On admission on July 12, 1956, he was a pale thin child but appeared active and well. In the abdomen an ill-defined mass could be palpated in the right renal area. The liver and spleen were not palpable. The cardiovascular, respiratory, lymphatic and central nervous systems were normal.

A straight radiograph of the abdomen showed a large calcified cyst, kidney-shaped, lying in the region of the right kidney (Figs. 1A and 1B).

A blood count gave a total white cell count of 12,000/c.mm. (polymorphs 50%, lymphocytes 36%, eosinophils 9%, monocytes 5%), Hb 86%, E.S.R. 5 mm. in one hour.

No albumin, sugar or acetone were found in the urine and in the deposit a few epithelial cells but no pus cells or red cells were seen.

Liver function tests were within normal limits.

The blood urea level was 38 mg. %.

A Mantoux test (1:1,000) was negative.

An intravenous pyelogram showed that the cyst was situated in the right renal area but did not involve the pelvis of the kidney (Fig. 2). The pyelogram of the left kidney was normal.

A provisional diagnosis of simple cyst or neoplasm of the kidney was made.

On July 16 Mr. Kirkman explored the right renal area through an oblique incision. A large cystic mass with an opaque firm wall adherent to the lateral aspect of the kidney, from which it appeared to arise, was found (Fig. 3). A right nephrectomy was performed.

Dr. K. W. Lodge reported that the specimen was a kidney measuring 9×2×4 cm. with an attached cystic mass 9 cm. in diameter.

On section the cyst was firmly adherent to the capsule of the kidney and was compressing the kidney tissue but not invading it. The cyst contained clear colourless fluid and had a thin wall in which there was a deposit of calcium and a smooth gelatinous lining. It was not

FIG. 1A.—Anterio-posterior radiograph of the right abdomen showing the cyst in the right renal area.

FIG. 1B.—Straight lateral radiograph showing the position of the cyst in relation to the right renal area.

in communication with the pelvis of the kidney and at the upper pole there was a multilocular area.

A portion of the attached ureter showed no abnormality. The cyst wall was composed of fibrous tissue lined by a layer of amorphous acellular material bordered by a single layer of flattened epithelium. The kidney adjacent to the cyst showed a marked inflammatory reaction in which the predominant cells were eosinophils. Attached to the cyst lining and in the kidney pelvis there were a few parasites which showed a peripheral capsule and a central area containing a sucker and invaginated hook-like structures. The appearances were those of a cyst containing parasites which closely resembled the *Echinococcus granulosus*.

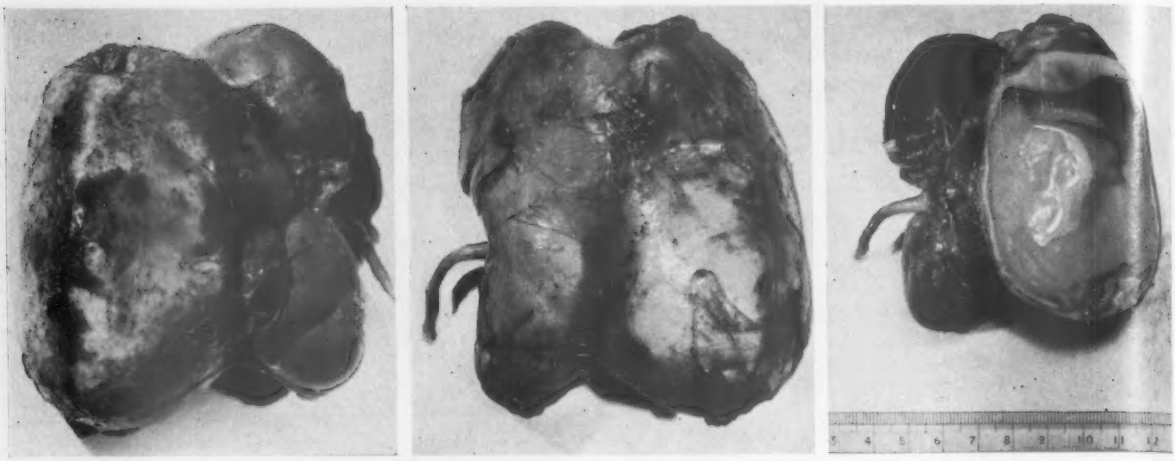
FIG. 2.—Intravenous pyelogram showing the cyst related to the right renal pelvis.

The child made a good post-operative recovery. A Casoni test performed on July 28 gave a negative result. Radiographs of the chest and long bones were normal. He was discharged on July 30, and on September 3 he was readmitted for cystoscopy when no abnormality was found in the bladder. The urine was examined for scolices, hooklets and hydatid material but none were found. The total white cell count was 7,200/c.mm (eosinophils 3%). Casoni tests were performed on his family and were negative. The child is being followed up as an out-patient and when seen last in December, 1956, was very well.

Discussion

There are several points of interest. It is probable that the pyrexia of unknown origin in 1952 was the reaction caused by the primary infestation of the echinococcus and would account for the high eosinophil count in 1952. It is interesting that the eosinophil count has fallen from 1,080/c.mm. to 216/c.mm. since operation.

The kidney was removed because the possibility of malignancy could not be excluded at the time and



(a) (b) (c)

FIG. 3.—Photographs showing views of the hydatid cyst and right kidney removed at operation: (*a*) Anterior view; (*b*) posterior view; (c) on section.

the mass was too adherent to the kidney to dissect it away completely. Even if the diagnosis had been made pre-operatively a nephrectomy is generally considered to be the treatment of choice for renal hydatid cyst. In this particular case hooklets in the pelvis of the kidney made nephrectomy essential.

The prognosis for the child is good, if it is a single cyst, and it is thought to be so. The cyst was completely removed and there was no evidence of spread down the ureter.

Summary

A short survey of the incidence of hydatid disease is given. A case of hydatid cyst of the kidney in a 7-year-old boy is described together with the relevant investigations and treatment. Certain points arising from the history are discussed.

I wish to thank Mr. N. F. Kirkman for permission to report this case and also for his helpful encouragement. My thanks are also due to Miss Gibbon, of the South Manchester Hospital Management Committee Department of Medical Illustration, for the photographs, and to the nursing staff of the Duchess of York Hospital.

REFERENCES

Baurys, W. (1952). *J. Urol.* (*Baltimore*), **68**, 441.
Bensted, H. J. (1957). Personal communication.
Dew, H. R. (1928). *Hydatid Disease*, pp. 27, 91. Australasian Medical Publishing Co., Sydney.
Gray, O. P. (1953). *Archives of Disease in Childhood*, **28**, 243.
Mackay, R. I. (1956). *Postgrad. med. J.*, **32**, 16.
Wolfe, H. R. I. (1943). *Lancet*, **1**, 795.

RADIAL NERVE PALSIES IN THE NEWBORN

BY

GEOFFREY V. FELDMAN

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(RECEIVED FOR PUBLICATION MAY 3, 1957)

Although usually omitted in the description of nerve injuries in the newborn, radial nerve palsies are not infrequent. The cause of the paralysis is not clear but the occasional coincidental finding of a patch of subcutaneous fat necrosis over the course of the radial nerve (Lightwood, 1951) suggests the possibility of direct trauma to the nerve.

That the injury is not uncommon is supported by the observation of seven infants born in St. Mary's Hospital, Manchester, since 1953 with radial palsy, and an eighth seen by Professor Morris. In view of the scant literature on the subject it was considered worth while recording these cases.

Case Reports

Case 1. A primigravida aged 22 years was admitted in labour. Her pains lasted for seven days and a female infant (L.B.) was delivered by normal forces 45½ hours after rupture of the membranes.

During the second stage of the labour a diagnosis of hypertonic uterine inertia was made and it was thought that a constriction ring was palpable at one stage.

The infant weighed 7 lb. 14½ oz. and although no abnormality was detected at birth, on the fourth day a right-sided wrist drop was noted. On the sixth day a small patch of subcutaneous fat necrosis was detected over the lateral aspect of the right upper arm in a position overlying the radial nerve.

Four and a half weeks after birth, during which time a cock-up splint and passive movements had been the treatment, practically full movement had returned to the wrist.

Case 2. A primigravida aged 23 years had a lower segment caesarean section following a prolonged labour with cervical dystocia. During labour the uterus was said to be very tense and difficult to palpate.

The infant (J.D.), a boy weighing 7 lb. 13 oz., required resuscitation and regular respiration was not established for 10 minutes.

No abnormality was noted at birth but on the sixth day a left-sided wrist drop was detected and a 'cock-up' splint applied. Six weeks after birth normal movement was present in the wrist.

Case 3. A primigravida aged 31 years was delivered by lower segment caesarean section on account of uterine inertia after a first stage of over 80 hours and premature rupture of the membranes.

The infant (M.R.), who was a girl weighing 8 lb. 8 oz., exhibited only irregular gasping respiration for the first 10 minutes and subsequently showed evidence of atelectasis and 'cerebral signs'.

On the day after birth a right wrist drop, associated with an area of subcutaneous fat necrosis over the lateral aspect of the right upper arm, was present. The radial palsy had completely recovered eight days after birth.

Case 4. After labour lasting 48 hours and complicated only by an intrapartum pyrexia, a primigravid woman aged 24 years gave birth to a female infant (A.W.) weighing 8 lb. who breathed spontaneously.

The infant was thought to be postmature. She had bilateral wrist drop. Three days after birth subcutaneous fat necrosis was present on the lateral surface of both upper arms.

Function of both wrists had fully recovered three months after birth.

Case 5. A primiparous woman aged 23 years suffered from uterine inertia in both the first and second stages of labour. On this account lower forceps extraction was carried out and an 8 lb. 3 oz. male infant (J.C.) was delivered.

The infant was asphyxiated at birth but rapidly recovered. He was found to have a right facial palsy and bilateral wrist drop. On the inner aspect of both upper arms and at corresponding sites on the sides of the chest, pressure marks were visible. The day after delivery patches of subcutaneous fat necrosis appeared on the chest walls at the site of the pressure marks and in addition a further small patch appeared just above the lateral condyle of the right elbow. During the subsequent three days the left wrist drop progressively improved but the right side showed no sign of recovery and the area of subcutaneous fat necrosis increased in size.

By the twelfth day normal movement had returned to the left wrist but although there had been considerable improvement in the right wrist, recovery was not complete until five weeks after birth.

Case 6. A primipara aged 23 years had a delayed second stage of labour, the total duration of her labour being over 138 hours. She was finally delivered with

the assistance of a low forceps extraction of a female infant (L.T.) weighing 6 lb. 12 oz.

The infant showed a large caput over the right brow with oedema of the eyelids on the right side. There was some evidence of atelectasis and bruising was noted over the middle of the lateral aspect of the left upper arm, a left wrist drop also being present. Subcutaneous fat necrosis developed on the arm at the site of the bruising. Five weeks after birth full movement had returned to the wrist and the fat necrosis was no longer detectable.

Case 7. A primigravida aged 30 years was delivered by normal forces of a female infant (J.M.) weighing 7 lb. 14 oz. A right-sided wrist drop and a patch of fat necrosis on the outer side of the right upper arm were noticed four days after birth, the left wrist also showing some weakness of extension. Three weeks after birth the wrists were moving satisfactorily.

Case 8. Professor W. I. C. Morris has kindly supplied the following description of a case of which he had care before coming to Manchester:

'In the spring of 1947 I attended, at the Western General Hospital, Edinburgh, a patient who was delivered by caesarean section of a living baby who showed a striking but temporary paralysis of the extensor muscles of its right wrist.

Labour was prolonged, lasting in all some 72 hours. The action of the uterus was irregular, but the extent of the disorder was not recognized until the third day, the house officer staff being lulled into a sense of false security by the fact that the membranes remained intact. The real facts of the situation were not recognized until I myself observed a slight sulcus which crossed the patient's abdominal wall at right angles to the long axis of the uterus at a level a little below the patient's umbilicus. This sulcus was constantly present. During active contraction of the uterus it became exaggerated, and a diagnosis of constriction ring was made. The infant was presenting by the head in the left occipito-lateral position. The infant was well grown, but there was no disproportion, the head having already passed the plane of the pelvic brim.

It was decided to carry out a caesarean section. When the abdomen was opened, the sulcus was easily visible on the anterior uterine wall as an area of annular spasm, with a number of greatly dilated subperitoneal venules radiating from it both upwards and downwards in the long axis of the uterus. The uterus was opened with a transverse incision in the lower uterine segment. The infant's right shoulder presented through the uterine wound, and it was necessary to pass the hand deeply into the pelvis to disimpact the head before the baby could be extracted. As this was done, it was noted that the scalp was uniformly oedematous to a degree which gave rise to an erroneous suspicion that the infant might be suffering from hydrops foetalis. He was in fact quite normal, and once the head had been brought out through the uterine wound, he was extracted quite readily. He cried at once. The operation was completed in the usual manner. The mother made a good recovery and the baby, too, did well.

When the infant was examined after delivery, he was found to have a dropped wrist on the right side. The back was crossed obliquely by an area of ecchymosis, faint but quite definite, extending from a point in the posterior triangle of the neck on the left side downwards and towards the right. Over the right superior extremity there was a faint ecchymosis of the skin on the lateral side of the arm, corresponding to the line of ecchymosis on the infant's back, and the contour of the arm was quite noticeably concave, the ecchymosis being situated quite precisely over the middle of the shaft of the humerus immediately over the line of the musculospiral nerve. The infant's body on the cephalic side of the line of ecchymosis was quite markedly oedematous, the oedema involving the thoracic wall, the neck and the whole of the vertex.

It was concluded that pressure from the annular spasm of the uterus was responsible for the line of ecchymosis, and that the dropped wrist might be attributable to direct pressure of the constriction ring on the musculospiral nerve. The oedema of the foetus was thought likely to be due to interference with the venous drainage from the skin attributable to the same spasm.

The baby was photographed three hours after delivery. Twenty-four hours later the oedema had disappeared. The dropped wrist persisted for a few days, but had cleared up when the mother went home on the twenty-first day.'

Discussion

In a review of the seven cases observed at St. Mary's Hospital, Manchester, no common factor, with the exception of the parity of the mother, comes to light. This could hardly be the direct cause of the injury.

However, with the exception of two cases, labour was prolonged and led to termination by abnormal means in four of these five cases, two by caesarean section and two by low forceps extraction. In two cases a diagnosis of hypertonic uterine inertia was made in both of which the presence of a constriction ring was suspected, and in a third the uterus was reported to be tense and difficult to palpate. That uterine inertia had occurred in a fourth case is known, though the tone of the uterus is not noted. Perhaps then Professor Morris's case may supply the clue to the causation of the radial palsy in these cases. There seems to be no doubt that from his description of the case the foetus had suffered pressure such as would be likely to cause trauma to the radial nerve. Could it then be that trauma of a similar type, though less obvious, has been the cause of the radial palsy in the four cases under review in which uterine inertia occurred? Certainly in Case 6 there had been sufficient intra-uterine pressure exerted to cause pressure marks and subsequent subcutaneous fat necrosis on the chest wall where the arms had been in contact.

Even in the two cases in which there was no evidence of uterine inertia subcutaneous fat necrosis had occurred at sites overlying the course of the radial nerve, suggesting the possibility of pressure at this site. In one of these the fat necrosis and wrist drop were bilateral, a fact much more easily explained by a concentric pressure exerted by the uterus than from pressure by other means in the birth canal. Is it therefore not possible that a transient hypertonic state had existed in the uterus though not sufficiently long lasting to cause inertia or delay in delivery?

The prognosis for the radial palsy was good in all the cases mentioned though full recovery took a varying period of time, this prognosis being consistent with the cases reported by Lightwood. It is interesting to note that the labour in the first of Lightwood's cases was prolonged, though terminating by normal forces.

It is therefore suggested as a possible hypothesis to explain the occurrence of radial palsy in the newborn that some such cases may be due to abnormal uterine action, causing constriction of the foetus's arm at the site of the radial nerve.

Summary

Eight cases of radial palsy in the newborn are described. Uterine action was known to be abnormal in six of these cases. The prognosis for the radial nerve lesion was uniformly good.

It is suggested that a uterine constriction ring may be a cause of such radial nerve lesions.

My thanks are due to Professor Wilfrid Gaisford for his advice and for allowing me to include cases under his care; to Professor W. I. C. Morris for his help in supplying information regarding his case, and to Dr. George Komrower under whose care were some of the cases described.

REFERENCE

Lightwood, R. (1951) *Archives of Disease in Childhood*, **26**, 436.

BRITISH ASSOCIATION OF PAEDIATRIC SURGEONS

The Fourth Annual Meeting of the British Association of Paediatric Surgeons was held in Edinburgh at the Western General Hospital, and the Royal Hospital for Sick Children, on June 6, 7 and 8, 1957, under the chairmanship of Mr. Denis Browne, the President. The meeting was attended by paediatric surgeons from many countries, including U.S.A., Sweden, Denmark, Poland, Belgium, Holland and Portugal.

At a meeting of the Council of the Association, it was decided that the president should be elected at the Annual General Meeting to take office from the following January 1, and should normally hold office for two years.

ELECTION OF OFFICERS FOR THE YEAR 1958. The following were elected:

PRESIDENT: Miss Isabella Forshall
SECRETARY: Mr. R. B. Zachary
TREASURER: Mr. P. P. Rickham
EXECUTIVE COMMITTEE: Mr. Denis Browne
Mr. W. M. Dennison

ELECTION OF MEMBERS. The following were elected:

MEMBERS OF COUNCIL

Mr. M. B. O'Donnell (Dublin), Mr. J. H. Johnston (Liverpool)

MEMBERS

Mr. A. D. R. Batchelor (Edinburgh), Mr. C. E. Fordyce (Middlesbrough), Mr. C. A. Ferguson (Glasgow), Mr. S. L. Mann (Glasgow), Mr. R. T. Campbell (Southampton)

OVERSEAS MEMBERS

Dr. J. Zucha (Bratislava), Prof. F. Soave (Geneva), Dr. J. G. Lestache (Madrid), Dr. Madrigal (Mexico City), Prof. J. Kossakowski (Warsaw), Dr. E. Drescher (Warsaw), Dr. W. Poradowska (Warsaw), Dr. Oberniedermeir (Germany), Prof. Raisch (Germany)

The following are abstracts from papers not to be published in full.

J. KIRK (Edinburgh). 'Wringer and Degloving Injuries.' The incidence of this type of injury appears to be increasing. The agents responsible may be encountered by the child both at home and on the roads, and may range from electric wringers to automobile wheels. The shearing nature of the strain applied to the soft tissues produces a similar basic lesion, though the clinical picture varies from a seemingly innocuous split in the skin to complete loss of skin and subcutaneous tissue.

The general principles of wound care are applied in wound treatment. There are several alternative methods of providing primary skin cover; the existing flaps are rarely viable, but in most cases free skin grafts are safer. These may be partial or full thickness, and obtained from the avulsed skin or a fresh donor site. In special instances immediate flap cover may be required.

Several cases were illustrated in demonstration of these injuries and their treatment.

D. W. SHANNON (Edinburgh). 'The Place of the Anaesthetist in the Management of Trauma in Children.' The child's high oxygen requirements lower his vital reserves. This is responsible for his rapid deterioration after injury. The clinical assessment of the rapidly changing picture should be based upon clinical observations.

Treatment should be directed against the danger of tissue hypoxia, aiming at increasing oxygen supply, improving oxygen transport to tissue and cutting down tissue demands for oxygen.

D. VERVAT (Rotterdam). 'Stenosis and Atresia of the Duodenum.' The causes of obstruction in the duodenum were described, and the diagnosis and clinical picture discussed. Therapeutic measures were discussed in the light of the pathological findings, and special attention was paid to pre- and post-operative measures, anaesthetics and technical problems.

D. VERVAT (Rotterdam). 'Biliary Atresia.' The causes of prolonged icterus after birth were described and the clinical and pathological manifestations discussed.

With reference to the work of Karrof and Donovan and a case of biliary atresia seen in the Children's Hospital in Rotterdam, the possibility of postnatal growth of bile ducts was considered.

HUGH B. LYNN (Louisville, Kentucky). 'Film on Duodenal Obstruction.' This film is a pictorial presentation of obstruction of the duodenum in infancy, including atresia, early and late symptomatic stenosis, and incomplete rotation with duodenal bands, etc. Radiographs and drawings are inserted as aids in orientating the viewer.

The surgical management of these conditions is the subject matter and follow-up visits are shown in most cases.

Emphasis is placed upon the incidence of mongolism associated with this condition. In this series the incidence of established mongolism has been at least 30%.

The association of a mobile caecum with the various forms of duodenal abnormality is pointed out.

I. S. KIRKLAND (Edinburgh). 'Acute Dilatation of Stomach.' Although now a rarity in surgical practice this is still a serious complication. The clinical picture presents these outstanding features: sudden enlargement of the stomach, large amounts of gastric aspirate, progressive dehydration.

Acute dilatation of the stomach has followed almost every type of operation and many other conditions, notably accompanying diabetic coma and dietary indiscretions. Pathological findings in fatal cases seldom

show any evidence of mechanical obstruction to the pylorus and duodenum. The aetiology is discussed together with observations on the quantities and analyses of fluid aspirated from the intestinal tract.

The clinical findings in patients with acute gastric dilatation are summarized and these illustrate the two forms in which the condition may present: (1) mechanical compression syndrome and (2) dehydration and electrolyte loss syndrome. The principles of treatment of such cases are outlined briefly.

H. H. NIXON (London). 'Agenesis of the Sacrum'. Eight cases of the isolated deformity were discussed. All were referred for urinary symptoms and had a neurogenic bladder disorder. The abnormality may not be clinically obvious and there may be no other neurological lesion demonstrable. Nevertheless post-mortem examination of one case revealed a myelodysplasia which was much more extensive than the skeletal defect.

The radiographs and records of 41 cases of imperforate anus or rectum were reviewed and radiographs of 25 other babies examined as controls. Half the cases of imperforate anus had sacral agenesis of some degree.

Of the cases of imperforate rectum only one-third had a normal spine, but of the remainder only half had true sacral agenesis. The remainder showed 'epistasis'. In this condition the apparent shortening of the sacrum to four segments is compensated for by an extra lumbar vertebra.

In true agenesis of the sacrum with loss of more than one segment bladder dysfunction is most likely, but in epistasis the bladder function will often be normal.

A. SMALL (London).'Operation for Cervical Sinus.' A cervical sinus is a considerably larger structure than is suggested by its minute external orifice, but removal beginning at its orifice may be difficult because of the extent of the dissection under the upper margin of the incision, and because the sinus, though substantial in size, is insubstantial in strength. As has been recognized, access to the upper portion is made easier by a supplementary incision over the bifurcation of the carotid (the 'step-ladder technique'). The sinus is defined and strengthened by the passage of a ureteric catheter, lubricated with vaseline. The dissection is completed up and down through the one incision.

GEORGE P. MITCHELL (Edinburgh). 'The Value of Arthrography in the Treatment of Congenital Dislocation of the Hip.' Straight *x*-ray examination of 'congenital dislocation of the hip' shows the degree of osseous aplasia but fails to reveal the cartilaginous outline of the acetabulum and femoral head.

The injection of radio-opaque fluid into the hip joint enables radiotranslucent structures to be visualized and provides further information about the different stages of dysplasia—predislocation, subluxation and dislocation.

Arthrography indicates to what extent the cartilaginous roof of the socket is deformed by the displacing femoral head and demonstrates the presence of any soft tissue obstacle which might prevent accurate reduction.

J. KOSSAKOWSKI (Warsaw). 'Unusual Causes of Trauma in Infancy.' The author gave a number of rare causes and circumstances of trauma in infancy, observed during 27 years of practice. Among other cases he quoted fire-arm injuries of foetuses in the womb; one of these children was born by caesarean section, then operated on and saved. Further he quoted cases of mortal injuries inflicted on newborn babies by young children; he gave instances of medical interventions performed by children on their younger brothers and sisters, and many other circumstances of unusual trauma which occurred in the course of children's games. The author found these cases not only unusual but also useful in psychological considerations concerning children of different ages, which may often help in preventing quite unexpected injuries.

J. KOSSAKOWSKI (Warsaw). 'The Indications for Caecostomy in Peritonitis and Intestinal Obstruction.' The author used caecostomy almost exclusively in unusual difficult and neglected cases of diffuse peritonitis or mechanical intestinal obstruction in newborns, infants and older children. The operation consisted in leading a thin rubber tube through an opening in the caecum and (most often after having removed the appendix) through the ileo-caecal valve (Bauhin) to the small intestine. The drain passed outside the operation wound through a small opening in the skin. Indications for this operation are: very serious and dangerous cases of adynamic obstruction in the course of peritonitis or unresolved mechanical obstruction, and also after resection and immediate anastomosis in infants. In the Warsaw Surgical Children's Clinic caecostomy has been performed over 50 times. Several times caecostomy followed an operation for peritonitis or intestinal obstruction when, in spite of the removed cause of the disease, the child's condition rapidly grew worse. The condition of all the children who had been operated on was very bad and there seemed to be no hope of keeping them alive; six children died after caecostomy.

C. P. STEWART (Edinburgh). 'Observations on Metabolic Changes Following Trauma.' The necessity of providing controls for the interpretation of blood and urine analyses in traumatized patients has meant that most of our knowledge of the metabolic changes following trauma has, in fact, been obtained by the study of surgical patients. However, it is clear, from a comparison of such studies with analyses after accidental trauma and from animal experiments, that there is one basic metabolic pattern representing the sequel to trauma in general, modified though it may be in individual cases by various factors such as the type and extent of the trauma, the condition and previous history of the patient, etc.

The main features are well known—a marked increase in protein oxidative breakdown, and alterations in the electrolyte balance strongly suggestive of increased secretion of adrenocortical hormones (which indeed ordinarily occurs).

Three of the many parts which make up this broad picture were discussed: the means of ensuring that the normal electrolyte changes do not become abnormal; the importance of the adrenocortical factor; and the changes in the plasma proteins.

BOOK REVIEWS

The Development and Disorders of Speech in Childhood. By MURIEL E. MORLEY. (Pp. 440. 45s.) Edinburgh and London: E. & S. Livingstone. 1957.

This is an altogether excellent book which fulfils a real need. It is a book which must be found a place in the library of every hospital caring for children, and on the shelf of every speech therapist. Paediatricians and others responsible for children will find it of great interest and of great value in their work.

The book contains sections on the development of normal speech, the delayed development of speech, defective articulation, stammering speech disorders in twins and lateral dominance. There is a useful chapter on the speech problems of cerebral palsy.

The book is soundly based on immense personal experience which has been most carefully recorded and analysed. It is full of sound commonsense and wisdom. Miss Morley makes appropriate comments on popular myths concerning tongue tie, laziness as a cause of speech retardation, psychogenic factors in speech retardation and speech being later in 'only' or 'first' children than others.

It is a really comprehensive valuable book which is likely to become the recognized classic on the subject.

There is only one omission. Miss Morley does not tell us how to distinguish a broad Tyneside accent from dyslalia.

Die heutige Behandlung der Skelett-Tuberkulose des Kindes und des Jugendlichen. By GEORG GLOGOWSKI. (Pp. viii+61; 54 figures. D.M. 10.80) Stuttgart: Thieme. 1957.

This short monograph considers bone tuberculosis in the light of the modern treatment available. The brevity of the presentation restricts any full consideration of diagnosis, complications or any particular treatment. The literature on the subject of bone tuberculosis is briefly considered and the clinical and therapeutic points made in the text are underlined by illustrative cases with elegant *x*-ray pictures.

The Normal Child, 2nd ed. By RONALD S. ILLINGWORTH. (Pp. xii+356; 68 figures. 35s.) London: J. and A. Churchill. 1957.

In this very readable book the author stresses the importance of the study of the normal child. He rightly avers that many trivial complaints regarding infants and young children are so common that they may be regarded as being within the range of normality. And yet, if the significance of these is not appreciated and the problems dealt with properly, the trivialities may become real problems for the infant and parents as well as the doctor.

The book is divided into four main themes—feeding, physical, developmental and behaviour problems. In discussing these various aspects of the normal child the author has been generous in quoting other authorities. It may be felt that there is a tendency to be rather too dogmatic in certain of his own opinions but he has been fair enough to give the opinions of others about many controversial points.

The cover states that the book has been designed for the use of all doctors who are concerned with the care of children. It should indeed be of invaluable help to them. There are many chapters, especially those on feeding and behaviour problems, which could be read with benefit by sisters and nurses who look after children. For undergraduate students the book should serve as a useful introduction to the study of paediatrics.

A Visit to the Hospital. By the staff of the Health Centre for Children. (Illustrated booklet. Free.) London. 1957.

Any attempt to reduce the psychological trauma to small children occasioned by their admission to hospital is worthy of study, and the Vancouver Health Centre, one of whose directors is Dr. Donald Paterson, has produced this very pleasant little booklet. It should provide pleasure for small children before the day of admission comes, and help the mother, through the medium of its attractive sketches of hospital life, to explain something of what her child will face when an in-patient. I believe that a booklet of this type might well help a child after his discharge to forget the less pleasant experiences, by reminding him of the lighter side. He might well count this book amongst his treasures long after his discharge.

The Medical Annual. Edited by SIR HENRY TIDY and PROFESSOR R. MILNES WALKER. (Pp. xl+570; 52 plates. No price given.) Bristol: John Wright. 1957.

The publication of circulation statistics has become a familiar form of advertising among newspapers and periodicals and, if this practice ever extends to medical books and journals, it seems probable that the *Medical Annual* will be very favourably placed. This year sees the 75th issue, which maintains the same form and high standard of its predecessors.

Articles from the recent medical literature of the world are reviewed in a series of brief notes, titled according to subject and arranged in alphabetical order. There are also four special articles including an exceptionally lucid account of the modern theory of blood coagulation.

In their introduction the editors remark that 'children's wards in hospital are half empty and many are being closed' and this belief probably accounts for the relative paucity of paediatric subjects in the text. This, of course, leaves more space for other specialties and thus enhances the value of the book to those who are already familiar with paediatric literature. They will learn with interest that infection with measles is acquired solely through the eyes (page 234) and among many other novel and interesting items there is an excellent review of some recent vital statistics.

THE TREATMENT OF OESOPHAGEAL ATRESIA*

BY

EINAR SANDEGÅRD

Lund, Sweden

Though both the anatomy and the symptomatology of the first cases of oesophageal atresia were described in detail more than 250 years ago, it was not until 1941 that the first child suffering from this anomaly was successfully operated upon. The mortality rate diminished rapidly during the following years, and, as methods making successful treatment possible were presented, a campaign was started to bring all cases of oesophageal atresia to the surgical wards as soon as possible after birth. That this has not been without effect is shown by the great number of cases now living which make a background to our evaluation of different methods of treatment.

Oesophageal atresia is a fairly common disease. The frequency is said to be 1 : 2,500-3,000 births. Both prognosis and selection of the method of treatment depend upon the type of malformation dealt with. According to Vogt's (1929) classification there are three principal types, namely, (1) complete absence, (2) atresia without tracheal fistula and (3) atresia with fistula between the trachea and the oesophagus, (*a*, those with a fistula between the upper segment and the trachea, *b*, those with a fistula between the lower segment and the trachea, *c*, those with fistulas between both segments and the trachea).

About 90% of all cases have a fistula from the lower oesophageal segment to the trachea and a blind-ending upper segment, that is, the type 3*b* of Vogt (Fig. 1).

In this connexion I should like to mention a further oesophago-tracheal malformation of which two cases have been recorded in Sweden during the last few years. In 1955, Pettersson, of Gothenburg, published one case where the upper parts of the oesophagus and trachea, including the larynx, were not separated from each other (Fig. 2). The child was operated on and is in good health. I also had a similar case a year ago. In this case, however, the oesophagus and the upper respiratory tract down to the carina were not separated (Fig. 2). An operation was performed through a left-sided cervical incision and a right-sided thoracotomy.

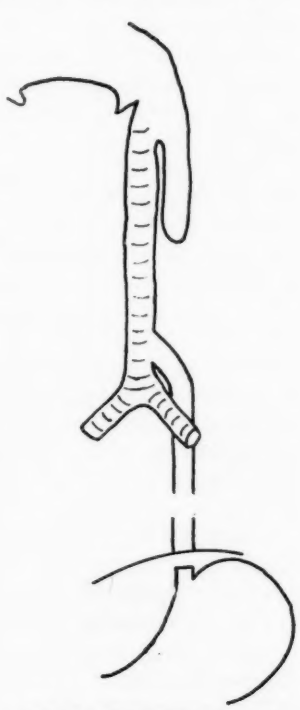

FIG. 1.—The common type of oesophagealatresia.

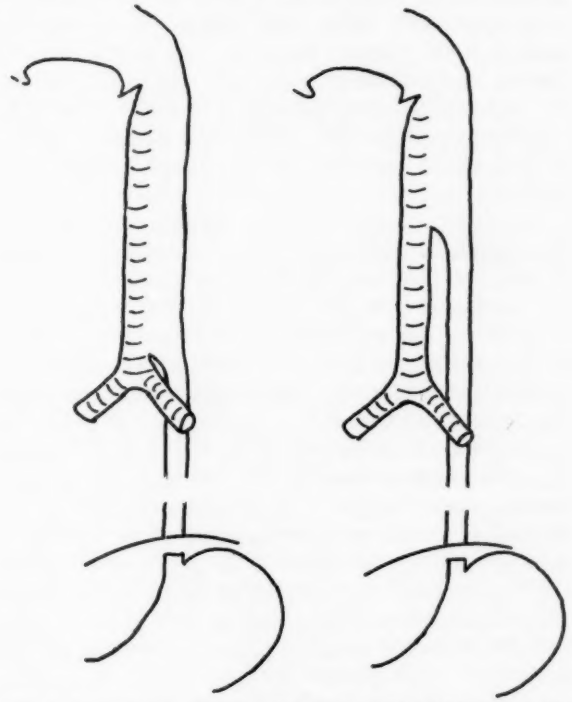

FIG. 2.—Oesophago-tracheal malformation with inhibited separation between the oesophagus and the upper respiratory tract.

* The Macarthur Lecture delivered at the annual meeting of the British Association of Paediatric Surgeons, 1957.

The patient survived the operation, which lasted eight and a half hours, and was performed with the help of a "narcos" respirator. The child remained in very good condition for a week in the respirator, but then unfortunately died suddenly from some unknown cause.

When the anatomical picture of the malformation is known it is not difficult to understand the clinical picture, and early diagnosis is easy. Characteristically the infant rapidly accumulates mucus in the nose and mouth, and suctioning of the mucus establishes normal breathing. Attempts at feeding are followed by coughing, choking and prompt regurgitation of all fluid given. These symptoms depend on the action of swallowing being blocked by the atresia. A catheter inserted into the oesophagus may demonstrate an obstruction, usually about 10 cm. from the lips. The diagnosis is verified by *x*-ray investigation after injection of some millilitres of 'lipiodol' through the catheter into the upper oesophagus. The 'lipiodol' should be sucked up after the investigation. Furthermore, the radiographs give valuable information regarding the extent of the pulmonary complications that in these cases usually can be diagnosed as atelectasis or pneumonia. Air in the gastro-intestinal tract indicates a fistula between the lower segment and the trachea. It may be added that it is necessary to remember that oesophageal atresia is often connected with other anomalies, of which congenital heart disease, malformation of the anus or rectum and atresia or stenosis of the small intestine are considered the most common. Sometimes the distribution of the air in the abdomen may suggest atresia of the bowel as an associated, complicating anomaly.

A review of the literature shows that the first important contribution to the surgical treatment of the oesophageal atresia was made by Richter in 1913. He gave a plan for the performance of the surgical procedure. This can be done in two different ways, either by closing the fistula and performing a direct anastomosis between the two oesophageal segments or by a multiple-stage procedure including closing the fistula, putting out the upper segment to a cervical oesophagostomy and making a gastrostomy. Later an oesophagus can be constructed. Richter operated on two children but both died.

Much hard work had to be done until Leven (1941) could report of the life of the first child saved through a multiple-stage procedure. Two years later the first case saved by a direct anastomosis was published by Haight and Towsley (1943). In Europe the first successful operations were reported by ten Kate (1947), Franklin (1948) and Sandblom (1948).

I should like to mention briefly the problems which have arisen during past years since the first successfully treated cases and keep mainly to atresia with fistula from the lower segment.

Since Mixter in 1936 advised the retropleural approach, the transpleural route seems to have been temporarily abandoned as being too dangerous. It became, however, quite natural after the advances in anaesthesia and thoracic surgery to try the transpleural exposure again, with the result that nowadays this method is the one commonly used. By both methods a right-sided approach has proved to be more practical than the one on the left.

The retropleural method means that the mediastinum is entered from a parascapular incision, usually after resection of the second or third down to the sixth ribs.

The transpleural exposure is made by entering the fourth or fifth intercostal space. When the incision into the mediastinal pleura has been made the operation continues in most respects in the same way as with the retropleural method. The azygos vein is divided, the vagus nerve is identified, the lower oesophagus dissected in its upper part and the tracheal fistula is divided and carefully closed. The upper oesophageal pouch is then mobilized and the anastomosis performed.

The disadvantage of the retropleural approach is that it does not easily allow a wide exposure of the mediastinum. The chief advantage, on the other hand, is that should the anastomosis break down the retropleural drainage may save the child and when there is only a partial rupture the anastomosis may heal spontaneously.

The disadvantage of the transpleural approach is that a post-operative insufficiency of the anastomosis may cause a pyopneumothorax which is a very serious complication, but this opening allows a wide exposure of the mediastinum which means that a better anastomosis can be performed. This is considered important as it has made the above mentioned complication rare.

However, several surgeons use the retropleural approach with very good results. Whether the exposure should be retropleural or transpleural is therefore a matter of opinion and still open to debate.

The anastomosis can be done by using one or two layers of interrupted sutures. Many surgeons prefer the Haight-Towsley technique, that is, suturing the whole thickness of the wall of the distal segment to the mucosa of the upper pouch and reinforcing the anastomosis by 'telescoping' the muscular layer of the upper segment around the lower one. With a couple of stitches Swenson (1947) attached the

upper segment to the prevertebral fascia as low down as possible in order to diminish the tension on the anastomosis. Sulamaa, Gripenberg and Ahvenainen (1951) fixed the upper pouch to the lower segment after having closed the oesophago-tracheal fistula without dividing the oesophagus. After that a termino-lateral anastomosis was performed. ten Kate used a flap from the upper segment for the anastomosis. In order to make sure that the anastomotic line is tight, Sandblom advised injection of saline solution in the upper oesophagus. If a leak could then be observed a closure could be done by one or two sutures more.

Without any doubt several of the various methods described in the literature can be used with success, but in all of them the important thing is to get a tight anastomosis without too much tension. This should be accomplished by a thorough mobilization of not only the upper segment but also as necessary of the lower one.

Often the lumen of the proximal part of the distal segment is very small. Increased diameter can be obtained by dilating it or by making a small longitudinal slit in the wall of the oesophagus. It is, however, well worth noting that even a quite narrow distal segment will usually dilate properly later.

In the first published series a relatively large number of patients had been treated by multiple-stage procedure. This might be explained by the fact that it was considered dangerous to free and mobilize the lower oesophageal segment to a desirable extent, the risk being insufficient nutrition and necrosis of the oesophagus. As it was often found at operation that a gap of several centimetres existed between the ends of the upper and the lower oesophageal segments, it is understandable that the multiple-stage procedure was often resorted to. However, it soon proved that this procedure meant a great deal of trouble and also carried a high mortality. Further, it became clear that the lower segment of the oesophagus could be freed much more than was earlier anticipated. Therefore it gradually became the usual practice to do a direct anastomosis in nearly all cases. It is now considered possible in all cases with oesophago-tracheal fistula. Those cases without fistula have as a rule a very short lower segment and it becomes necessary to pull the stomach up into the chest if a direct anastomosis should be done. However, at the moment there is no agreed method among surgeons. Thus Gross (1953) gave up the multiple-stage procedures in 1945 and prefers drawing the stomach up into the chest when necessary for making it possible to perform a primary anastomosis. Others have, however, tried this method without being able to achieve satisfactory results. Several other methods have been tried in these cases. Thus Sandblom in 1947 tried to construct part of the intrathoracic oesophagus by the transverse colon in a 4-day-old child. The child died. At the last meeting of the British Association of Paediatric Surgeons, Waterston demonstrated excellent results having constructed the intrathoracic part of the oesophagus from a loop of the colon.

Another question is, Should a gastrostomy be performed or not? It has been shown that oral feeding may be started a few days after the primary repair of the oesophagus. It is known that some surgeons keep a small catheter leading from the oesophagus to the stomach after the operation and feed the child through it. It seems, however, that most surgeons still prefer the gastrostomy as the safest procedure. As a matter of fact it can hardly be denied that a gastrostomy gives the best opportunity for the undisturbed healing of an oesophageal anastomosis and I suppose nobody can be seriously criticized if he always used a gastrostomy for feeding the child during the first 10 days post-operatively.

Blood and fluids should be given during operation in accordance with principles generally accepted in order to compensate losses and prevent shock. It has, however, been clarified that the operation represents only part, although an important part, of the treatment, and it might be correct to say that the adequate pre- and post-operative care of the child is the key to a successful outcome.

During the last 10 years many details have been emphasized in the treatment of these children. It is but natural that the early recognition depends on the alertness of those who have to treat the newborn babies. Those persons must also be acquainted with the treatment necessary to save the children from the immediate dangers. It is obvious that it is necessary to aspirate mucus from the pharynx of the child when there is excess and this ought to lead to a suspicion of the diagnosis. At the same time this is the first treatment. After that comes the steps taken in order to avoid complications. Suction should be repeated every quarter to half an hour if needed and feeding by mouth should be stopped. The child ought to be placed in a half-prone position in order to avoid regurgitation and aspiration of gastric contents.

If the preliminary diagnosis has been made shortly after birth and the child is in good condition there is no need for administration of parenteral fluids before the child is taken to a surgical department. In all cases it seems wise to start treatment

with antibiotics and to give vitamin K prophylactically.

When the patient is being transported, the person accompanying the child must be in a position to provide suction.

When the patient has been admitted to the surgical department and diagnostic measures are completed, treatment has to be decided upon. It must then be clear that though the case itself may be described as an emergency, it does not mean that the operation should be carried out immediately. On the contrary, under a diligently-performed prophylaxis against aspiration, a child who on admission is seriously ill can be brought into good condition and be given a fair chance to withstand the surgical procedure.

One way to establish this pre-operative care is to place the child in an incubator with the temperature controlled in saturated humidity. The pharynx is sucked out every quarter of an hour if needed. Oxygen is given when indicated. Treatment with antibiotics is continued or instituted if not given earlier. When indicated the child is given fluids parenterally, keeping in mind the warning against overhydration. We have followed Gross's advice to give 10% glucose in water intravenously to combat any existing ketosis. The amount should not exceed 20 ml. per kg. body weight every 12 hours. Generally this pre-operative treatment for a few hours will be enough; it may be given for 12 to 24 hours or even longer when the infant is in bad condition.

After the operation the child is brought back to the incubator which is properly warmed and humidified. There the child lies quite naked and it is possible to make continuous observations regarding its way of moving and breathing and its colour. Often the pharynx has to be sucked out frequently during the first few days. After that the child apparently is often able to swallow most of its saliva. Treatment with antibiotics is continued until the pulmonary complications are under control. In former years the administration of oxygen during several days post-operatively had been advised. Today we prefer to use only air in the incubator routinely. Humidity seems to be of the greatest value in the treatment and prophylaxis of pulmonary complications. The child must be kept from being overhydrated, and the parenteral fluid regulated, starting with about 60 ml. per kg. body weight per day and increasing gradually under weight controls. Gastrostomy feeds are started about 24 hours after operation and are as a routine continued for eight to 10 days. An *x*-ray investigation is then done and if it shows a good passage without fistula oral feeds are initiated. The gastrostomy tube is kept in for six to eight weeks. If there is no stenosis demonstrable the tube is then removed. After that the gastrostomy will usually close spontaneously.

In spite of the fact that the frequency of complications is diminishing due to safer methods of operation and better understanding of the pre- and post-operative care, we must always be prepared to face complications from the respiratory tract. Repeated radiographs are often necessary to determine the therapeutic effect on atelectasis and pneumonias. Repeated suction of the trachea and the bronchi may be necessary to eliminate a stagnating secretion which might otherwise rapidly kill the infant. Thus team work between the nurses, surgeons, anaesthetists and radiologists is necessary for the achievement of a good result.

In a certain number of cases stenosis of the anastomotic line develops, sometimes early in the post-operative course and sometimes later. This complication is usually not very dangerous if observed and treated by dilatation.

The most feared complication is of course rupture of the anastomosis. Sometimes it ruptures partially and may gradually develop into a pyopneumothorax, sometimes, however, the child deteriorates quickly.

I am unable to discuss the merits of different methods of anaesthesia in oesophageal atresia. Our anaesthetists have, in several cases, avoiding intratracheal tubes, administered cyclopropane-oxygen mixture through a tightly fitting face mask. We have thought this procedure less irritating for the larynx, but I know that there is no agreement about the advantages of this method.

Regarding the unusual types of oesophageal atresia, we have treated a few cases with rather disappointing results. However, at an analysis of these cases I have found nothing worth adding to that mentioned earlier.

In order to give an idea of the effect of our treatment I should like to show our results during the last five years (Table 1). The series consists of all cases of oesophageal atresia treated during that

TABLE 1
105 CASES OF OESOPHAGEAL ATRESIA

1951-1956	Number	Not Operated	Deaths	Mortality (%)
Atresia with fistula from the lower oesophageal segment	94	4	37	41
Other types of atresia	11	—	9	82
Total	105	4	46	44

time at the Carolina Hospital, Stockholm, the Crown Princess Louisa's Hospital, Stockholm and at the University Hospital, Lund.*

From Table 1 it is apparent that of 105 cases 101 have been operated upon with 46 deaths. That is an overall mortality of 44%. Ninety-four cases belonged to the group of atresia with fistula from the lower segment with a mortality of 41%. Eleven cases having some other type of the malformation were treated with a high mortality rate. The poor results in this small group show that we have not found a satisfactory method for these cases.

When discussing the results and the possibilities of getting better results, it has to be borne in mind that this series consists of many unfavourable cases. Among the factors of importance for the prognosis there are three uncontrollable factors. The first one is the type of anomaly, the second one is the degree of immaturity and the third is the presence or absence of associated anomalies. It is well known that these factors greatly affect the prognosis. Thus it will seem adequate when estimating the results to divide the series into the following groups shown in Table 2.

It is not astonishing to find a high mortality rate among the immature infants weighing less than 2,500 g., nor among those with serious associated anomalies. However, some of these anomalies can be corrected and others may be of minor importance for the immediate result. Therefore a certain number of these cases survive. Table 2 shows that among the cases of atresia with fistula between the lower segment and the trachea those with a weight of more than 2,500 g. and with no associated anomalies have a survival rate of 82% (the mortality rate 18%). This is gratifying as all those children can be expected to develop into functionally normal individuals.

* The series from the Carolina Hospital (62 cases) has kindly been put at my disposal by Th. Ehrenpreis and N. O. Ericsson, and the cases (23) from the Crown Princess Louisa's Hospital by G. Ekström.

TABLE 2

ATRESIA WITH FISTULA FROM THE LOWER OESOPHAGEAL SEGMENT, 1951-1956

	Weight	Number	Not Operated	Deaths	Mortality (%)
No associated anomalies	> 2,500 g.	44	—	8	18
	< 2,500 g.	20	1	11	58
With associated anomalies	> 2,500 g.	19	2	11	65
	< 2,500 g.	11	1	7	70
Total ..		94	4	37	41

REFERENCES

Franklin, R. H. (1948). *Ann. roy. Coll. Surg. Engl.*, **2**, 69.
Gross, R. E. (1953). *The Surgery of Infancy and Childhood*, p. 80. Philadelphia.
Haight, C. and Towsley, H. A. (1943) *Surg. Gynec. Obstet.*, **76**, 672.
Kate, J. ten (1947). *Maandschr. Kindergeneesk.*, **15**, 417.
Leven, N. L. (1941). *J. thorac. Surg.*, **10**, 648.
Mixter, C. G. (1936). *Ann. Surg.*, **103**, 736.
Pettersson, G. (1955). *Acta chir. scand.*, **110**, 250.
Richter, H. M. (1913). *Surg. Gynec. Obstet.*, **17**, 397.
Sandblom, P. (1948). *Acta chir. scand.*, **97**, 25.
Sulamaa, M., Gripenberg, L. and Ahvenainen, E. K. (1951). *Ibid.*, **102**, 141
Swenson, O. (1947). *Surgery*, **22**, 324.
Vogt, E. C. (1929). *Amer. J. Roentgenol.*, **22**, 463

HEPATIC HAEMORRHAGE IN THE NEWBORN*

BY

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Incidence of Hepatic Haemorrhage

It has long been known that injury to the abdominal viscera may cause stillbirth or death in the first days of life. Information about bleeding from the abdominal viscera has been obtained largely from post-mortem examinations of stillborn babies and babies dying shortly after birth. The incidence of bleeding from the liver estimated in this way is shown in Table 1. Hepatic haemorrhage is, therefore, the direct cause of or a significant factor in

TABLE 1
HEPATIC HAEMORRHAGE IN STILLBIRTH AND NEONATAL DEATH

Author	Incidence at Necropsy
Palmer (1928)	5 in 99
Cruickshank (1930) ..	18 in 800
Holmberg (1933) ..	56 in 1,000
Rogers (1934)	53 in 1,046
Potter (1940)	24 in 2,000
Henderson (1941) ..	47 in 1,312

determining from 1·2 to 5·6% of stillbirths and neonatal deaths. While this paper is concerned with hepatic bleeding, haemorrhage in other abdominal viscera is also important as a cause of stillbirth and neonatal death and the frequency with which the various viscera are affected is shown in Table 2.

TABLE 2
SITES OF ABDOMINAL HAEMORRHAGE IN STILLBIRTH AND NEONATAL DEATH

Viscus	Lundquist (1930)	Henderson (1941)
Liver	19	47
Suprarenal	17	30
Renal	—	25
Gastro-intestinal	—	32
Unknown	12	—
Spleen	1	—
Other viscera	—	10

The liver is the site of 39% and 32% of the intra-abdominal haemorrhages in these two series of cases.

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

Aetiology and Pathology

Lundquist (1930) recorded 19 cases of hepatic haemorrhage; 14 were subcapsular haematomas and five showed rupture of the liver parenchyma. He believed, therefore, that trauma was not important and suggested that subcapsular haematoma was the result of asphyxia. In Henderson's (1941) 47 cases, there was rupture of the liver and intraperitoneal haemorrhage in 24. Nearly half of the cases were complicated by intracranial haemorrhage. Henderson emphasized that rupture of the liver occurred in 18 out of the 32 stillborn cases (56%) and in six of the 15 (40%) babies born alive so that trauma played a greater part in the stillborn. He suggested that bleeding arises from contusion or laceration of the liver parenchyma; the capsule is then elevated by the haematoma which may become very large. Rupture of the capsule may follow because of tension or from handling the baby. Henderson found that the incidence of hepatic haemorrhage was much greater in premature and abnormally large babies than in those in the range from 5½ to 8 lb. in weight.

Surgical interest is centred in the babies who are born alive and more particularly in those who survive long enough for the diagnosis to be made. Henderson found records of 55 such cases in the literature and only one survived longer than a week. The only recovery followed operation on a Chicago baby recorded by Rogers (1934).

Potter (1940) recorded 24 cases in babies born alive and drew attention to the undoubted fact that many appear to be normal for the first few days but die suddenly in severe shock. Arden (1951), like Henderson, was impressed by the frequency with which post-mature babies are affected.

Arden, Dique and Wrench (1955) found that the babies fare normally for 48 hours and suggest that during that time they have a subcapsular haematoma which expands and ruptures. They believe that the condition is traumatic in origin but the massive bleeding is out of all proportion to the trivial liver damage and factors such as anoxia or prothrombin deficiency are the cause of the continuing bleeding.

Prognosis

Only one of the cases in the various series quoted previously survived. Stein and Wright (1953) reported 15 cases of liver rupture in babies born alive and none survived. Henderson's series of cases from maternity hospitals in Edinburgh showed no survivors in the seven-year period ending in 1940, and I am not aware of any since that date. Arden (1946) reported the successful treatment of a 2-day-old baby by suture of the liver capsule to the parietal peritoneum and later (1951) recorded six cases encountered in seven years, in four of which the diagnosis was made on clinical grounds. Shock developed with great suddenness from 36 to 104 hours after birth. Two of the babies died within 10 minutes, two recovered following transfusion and two following transfusion and laparotomy. Five of the six babies were post-mature. Greaves (1955) reported the case of a 2-day-old baby who became pale and collapsed. Straight radiographs in the erect and lying down positions showed no abnormality although the author felt that in retrospect when the diagnosis was known the shadows were denser than normal. He was able to find only six instances of survival in the literature and his patient also recovered following laparotomy and suture of a 1 in. tear in the substance of the liver. He advocates location of the bleeding site and its control by surgery.

Bret, Jamain and Coupé (1956) record three cases of haemoperitoneum following rupture of subcapsular haematoma of the liver with one recovery.

It seems that the prognosis is better following operation, but Arden advises conservative treatment despite his surgical success because (*a*) blood in the peritoneal cavity appears to do no harm to the baby; (*b*) the wound in the liver parenchyma may be difficult to find even if the site of the bleeding is readily accessible; (*c*) the capsule of the liver is unable to hold sutures at this age; and (*d*) the site of the bleeding may not be accessible. With adequate transfusion, but not overloading, the bleeding should stop but to be successful both surgical and medical treatment are dependent on the diagnosis being made in time.

Clinical Features

The clinical features described by Arden are well shown in the following case.

Female baby (J.M.), expected date of delivery October 19, 1954. At one week intervals thereafter induction was attempted but delivery, which was spontaneous, did not occur until November 13, 1954. There was great difficulty with the shoulders, and the baby, which was said to weigh 11 lb. 4 oz. (5·1 kg.), was somewhat shocked and required resuscitation. The baby became progressively lethargic but of good colour. On the fourth day she became very pale and quiet and would not suck. She was referred to hospital.

Examination showed a post-mature infant of 9 lb. 14½ oz. (4·5 kg.) with marked pallor and slight jaundice. Bruising of the left arm, dilated upper abdominal veins and a large ill-defined swelling in the epigastrium were noted. The abdominal mass was dull on percussion, the dullness being continuous with that of the liver. The spleen was not palpable. The abdomen also showed some general distension with dullness in the flanks. The baby vomited on the journey to hospital and this symptom persisted following admission. Blood examination, apart from 50% haemoglobin, showed no abnormality. Straight radiographs of the abdomen and left arm were taken. There was rapidly increasing pallor and abdominal distension and a surgical opinion was asked. The findings were those of a severe intraperitoneal haemorrhage. The radiographs (Fig. 1) indicated the presence of free fluid in the abdominal cavity and the clinical features were those of a hepatic haemorrhage. Rapid transfusion was begun and after 150 ml. had been given laparotomy was carried out. There were large clots and much dark blood in the peritoneal cavity. There was a very large ruptured subcapsular haematoma on the anterior surface of the liver with very active bleeding. Clots were removed and the bleeding found to be coming from a laceration of the liver parenchyma about 4 cm. long. The bleeding was controlled by suture of the liver followed by suture of the capsule. Much further clot was removed by suction and measurement of the fluid blood and clot indicated that at least 350 ml., and probably over 400 ml., of blood had been lost into the peritoneal cavity. Transfusion was continued rapidly until 400 ml. had been given.

The baby's condition was greatly improved and two days later she was feeding well, appeared to be normal and the haemoglobin was 100%.

At 2 months the baby was thriving and there was no evidence of other birth injury. The liver showed no abnormality on palpation.

From the hospital records this is the only baby in which the diagnosis has been made clinically and treatment has been successful. It is likely that rapid transfusion of a sufficient amount of blood would be successful without operation. It is certain, however, that without operation this amount of blood would not have been given over such a short period. Contrary to the view expressed by Arden the liver parenchyma held stitches well as did its capsule and the active bleeding was readily controlled.

It is difficult to accept the unqualified statement that bleeding into the peritoneal cavity does not upset the baby, for in my experience massive intraperitoneal bleeding has resulted in ileus and in our patient intestinal obstruction was suspected initially.

Quite apart from the theoretical value of the control of haemorrhage, operation may be advisable because an absolute diagnosis cannot be made without

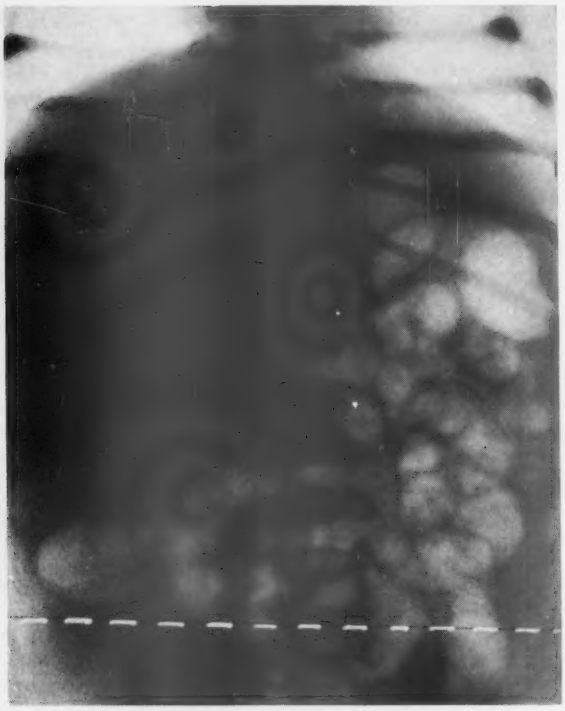

FIG. 1 (*a*).

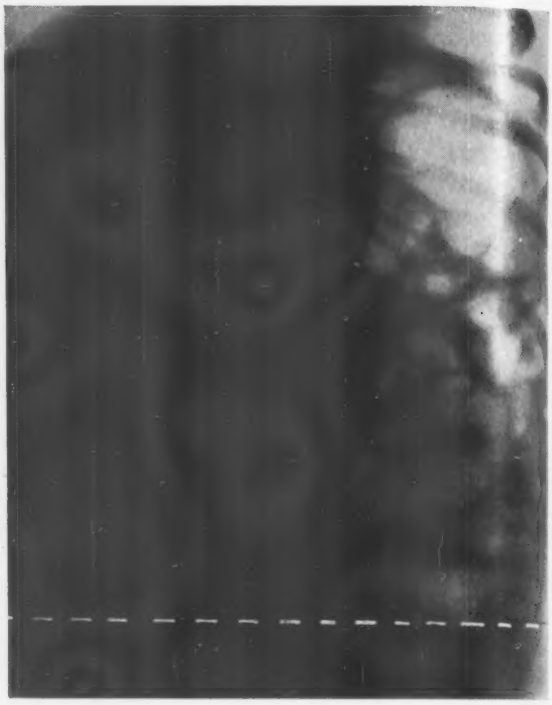

FIG. 1 (*b*).

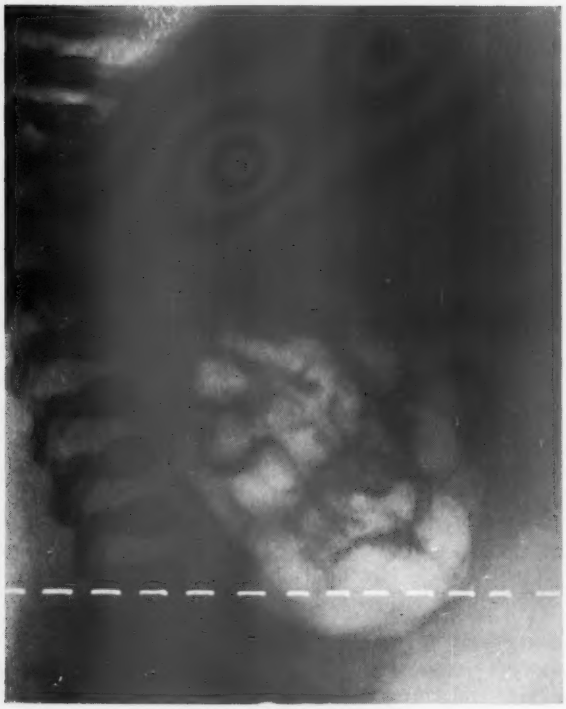

FIG. 1 (*c*).

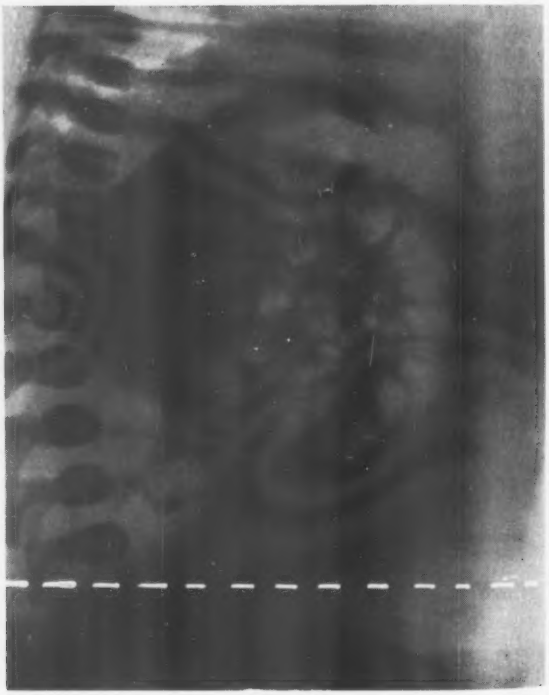

FIG. 1 (*d*).

FIG. 1.—Plain antero-posterior radiographs in the supine (*a*) and erect (*b*) positions. Plain lateral radiographs in the supine (*c*) and (*d*) erect positions.

Note that the assumption of the erect position has caused the intestine to rise to a higher level. This can happen only when it floats upwards on viscid free fluid such as blood. The white dotted line is at the level of the highest point of the iliac crest.

it. Dennison (1957), having treated a baby with rupture of a subcapsular haematoma of the liver by operation with success, encountered a second patient in whom the clinical diagnosis of liver haemorrhage was made but laparotomy revealed an unsuspected intussusception.

The risk of laparotomy in the newborn is now so small, the few cases of neonatal hepatic haemorrhage treated surgically have done so well and the difficulty of making a certain diagnosis without laparotomy all suggest that operation should not be lightly discarded. The presence of intraperitoneal bleeding may be indicated by the comparison of the level of the intestine in radiographs taken in the supine and erect positions.

As long as there is no method of treating an anomaly or disease its recognition is not important. Now that we can treat some cases of hepatic haemorrhage successfully greater attention must be given to the clinical features of subcapsular haematoma in the hope that the condition may be recognized before it ruptures into the peritoneal cavity.

If the diagnosis of subcapsular haematoma is made and the baby is kept under observation death may occur so rapidly that there is no time for treatment by transfusion. The treatment in such circumstances would seem to lie between immediate transfusion and the administration of vitamin K, or the same treatment plus laparotomy. Operation would be of value only if the haematoma were in an accessible situation. In his careful analysis Henderson found the site of the haemorrhage to be as follows:

SITE OF BLEEDING IN HEPATIC HAEMORRHAGE (HENDERSON, 42 CASES)

Superficial	Anterior and antero-lateral surface right lobe	21
	Anterior surface both lobes	3
	Anterior surface left lobe	11
Deep	Visceral surface right lobe	4
	Visceral surface left lobe	1
	Visceral surface ? lobe	3
	Postero-superior surface right lobe	3

It is obvious that the majority of haematomas of the liver will be readily accessible to the surgeon. While all the recorded cases treated surgically have recovered it does not prove that operation is the best treatment, for it may be that the babies who survived were those with delayed rupture of the haematoma or with the slowest rate of blood loss into the peritoneal cavity while failure of surgical treatment may not have been recorded. The diagnosis should be suspected when there is evidence of pallor and a falling haemoglobin with otherwise normal blood findings and in all cases of sudden collapse in the first days of life. There may be also a palpable swelling in the vicinity of the liver or obviously continuous with it. If the baby is premature or post-mature additional support is given to the diagnosis.

Summary

Trauma during delivery may cause liver injury especially in premature and post-mature infants.

A subcapsular haematoma is formed and rupture of the capsule of the liver follows immediately or is delayed for a few days.

The continuing bleeding is more severe than would be expected from the damage to the liver parenchyma alone and asphyxia or prothrombin deficiency may be responsible.

Rupture of the capsule may be followed by bleeding of such severity that death occurs within minutes before treatment can be begun.

The diagnosis of subcapsular haematoma of the liver can be made clinically in some cases and should be suspected in all cases of pallor and falling haemoglobin with otherwise normal blood findings. As rupture appears to be certain treatment should be begun before the subcapsular haematoma erupts through the capsule.

Straight radiography may be of value in establishing the diagnosis of free blood in the peritoneal cavity.

Transfusion is the most important therapeutic measure. The amount of blood required is likely to be underestimated. Surgical control of the bleeding may be difficult and may be unnecessary but operation may be valuable in estimating the amount of blood loss and in excluding other conditions requiring operative treatment.

It is possible that the successes following operation have been due to the undoubted fact that the babies coming to operation have been those in whom rupture was delayed and blood loss was less rapid, giving more time for the making of the clinical diagnosis.

A case of hepatic haemorrhage is recorded in which surgical arrest of bleeding from the ruptured liver was readily secured and measurement of the blood in the peritoneal cavity was invaluable in the control of the blood replacement.

REFERENCES

Arden, F. (1946). *Med. J. Aust.*, **1**, 187.
——— (1951). *Ibid.*, **2**, 632
———, Dique, J. C. and Wrench, D. (1955). *Ibid.*, **2**, 765.
Bret, J., Jamain, B. and Coupé, C. (1956). *Arch. franç. Pédiat.*, **13**, 1043.
Cruickshank, J. N. (1930). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 145, p. 60.
Dennison, W. M. (1957). Personal communication.
Greaves, J. L. (1955). *Lancet*, **2**, 1227.
Henderson, J. L. (1941). *J. Obstet. Gynaec. Brit. Emp.*, **48**, 377.
Holmberg, E. (1933). *Finska LäkSällsk. Handl.*, **75**, 1067.
Lundquist, B. (1930). *Acta Obstet. Gynec. scand.*, **9**, 331.
Palmer, A. C. (1928). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, **118**, 67.
Potter, E. L. (1940). *J. Amer. med. Ass.*, **115**, 996.
Rogers, G. (1934). *Amer. J. Obstet. Gynec.*, **27**, 841.
Stein, F. E. and Wright, L. T. (1953). *Harlem Hosp. Bull.*, **6**, 32. Quoted in *Yearbook of Pediatrics*, 1954-1955, p. 26.

TRAUMATIC INTRAMURAL HAEMATOMA OF THE PROXIMAL JEJUNAL LOOP*

BY

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That injury to the abdominal viscera can result from a blow by a blunt object on the abdominal wall has been recognized from the earliest days of medical knowledge; and that such a blow can leave no visible trace upon the skin of the abdominal wall was also known at that time. For, in the third century B.C., Aristotle is reputed by Morgagni (1761) (Epistola, quoted by Poer and Woliver) to have written that 'A slight blow will cause rupture of the intestine without injury to the skin'.

Poer and Woliver (1942) reviewed the literature of injuries of the intestines and mesenteries due to non-penetrating abdominal trauma and found numerous references in the literature from 1875 onwards, thus proving the continual occurrence of such injuries. These authors stressed the importance of early diagnosis, for all the cases reported up to that time were associated with rupture of the intestines or with injuries to the mesenteries. A mortality of 35% was found in those cases which were diagnosed and treated by operation at an early stage. For those in which there was a delay of over 12 hours the mortality rose to 70%.

Counseller and McCormack (1935) also published a survey of subcutaneous rupture of the intestine. Seventy-seven of the 1,183 cases found in the literature up to that time occurred in children under the age of 12 years. At all ages the jejunum was most often involved (447 occasions) and the ileum slightly less often (412 cases). In 29 instances the site of injury was either not noted or no perforation was found at laparotomy. In this group there may have occurred cases of haematoma of the bowel wall not considered worthy of note or record.

In yet a third and even earlier survey (Vance, 1923), it was stated that the jejunum and ileum were about equally involved in injuries of the subcutaneous type, and that the most frequently affected sites were those of natural fixation in the duodeno-jejunal area and the ileo-caecal junction.

It was not until 1952 (Zabin, 1952) that haematoma of the bowel wall as the cause of an acute surgical condition was cited. A boy of 4 years was struck in the left upper abdomen by the handlebar of a bicycle, and within six hours was complaining of abdominal pain. This symptom only became severe enough to warrant his admission to hospital two days later. A small abrasion of the abdominal wall was discerned at the site of impact with the handlebar. The significance of the injury was not appreciated and a pre-operative diagnosis of acute appendicitis was made. At operation there was a large amount of blood-tinged free fluid in the peritoneal cavity. A lower loop of jejunum, 14 in. long, lying in the left hypochondrium was found to be the site of a large haematoma. Resection was performed. The haematoma was found to lie under the circular muscle layer. The child recovered.

In 1954, Lampert, Goodfellow and Wachowski reported the case of a lad of 15 years who received a kick in the abdomen during a game of basketball. Although complaining of abdominal pain he was not admitted to hospital until two days later and there a further two days elapsed while obstructive symptoms and signs became more marked and the presence of an urgent abdominal condition quite definite. At operation a subserosal haematoma immediately distal to the duodeno-jejunal junction was found. The clot was evacuated from the bowel wall and recovery ensued.

During the last 10 years in the Royal Hospital for Sick Children, Edinburgh, four cases of jejunal injury without external evidence of violence have been admitted. Two of these, in girls of 8 and 5 years respectively, were associated with perforation of the gut; the first of the second loop of jejunum and the other of a lower loop. The first child had fallen on the high step of a barn; the second was squeezed by the rear wheel of a reversing G.P.O. mail van. In each case operation was performed within six hours of injury and recovery of both ensued.

The other two cases are of greater interest.

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

Case Reports

Case 1. On April 29, 1947, E.H., a boy of 9 years, fell off a tricycle which he was probably far too big to be riding. The handlebars struck him in the left upper abdomen. He immediately complained of pain and a bruise developed at the point of impact. Two days later, having carried on more or less normally in the meantime, he came home from school looking very pale and shortly afterwards he vomited several times. He complained of pain in the abdomen on vomiting and he continued to vomit everything he drank, the vomits soon becoming dark green. His bowels, however, continued to act, having last done so on the day before his admission five days after injury.

On examination of the abdomen, the respiratory excursion was moderately good. There was no acute tenderness on palpation but some guarding was appreciated in the upper left zone. The result of the examination was rather indefinite, but operative exploration was arranged after gastric aspiration had been instituted and his dehydration and shocked state improved by intravenous plasma and saline infusion.

At operation, through an upper right paramedian incision, no free fluid or blood was found in the peritoneal cavity. All the loops of small intestine which were immediately visible were noted to be tightly contracted and collapsed. A large tense, grossly distended loop of jejunum was felt in the upper left quadrant. This was found to be the first loop of jejunum. It was black, distended to approximately the size of a 'black pudding', and had a sharp demarcation between bowel of normal colour. The serous coat had not lost its sheen and the bowel was felt grossly thick to the touch. In delivering the loop, a small tear of the serous coat resulted and there was an immediate escape of blood and blood clot, but no faecal matter was evident. The glands in the mesentery of this loop were enlarged and there was also some formation of haematoma in the mesentery, in which the blood vessels were felt to pulsate normally. The affected loop was resected. This left insufficient normal gut to make an anastomosis possible. The short upper jejunal loop was closed and invaginated with some difficulty owing to its proximity to the duodeno-jejunal flexure. The lower loop of bowel was also closed and a posterior gastro-jejunostomy performed between it and the stomach.

Immediate examination of the specimen showed a portion of jejunum approximately 8 in. long. It was grossly distended. Normal bowel ended abruptly both above and below in purplish-black discoloration of the gut. The gut wall was thickened and felt solid. The specimen was cut after fixation in formalin and it was found that the lesion consisted of haemorrhage into the subserous coats of the gut wall. The large amount of blood had clotted and had stripped the mucosa and so compressed it that only a minute lumen remained. More detailed examination showed that the wall of the bowel had been disrupted by haemorrhage chiefly in the submucosal area, a large mass of recently clotted blood separating the mucosa from the muscular coats (Fig. 1). The mucous membrane and the muscularis mucosae were remarkably normal in appearance, there being a little congestion of the villi. The effused blood was mainly in the outer part of the submucosa. Some veins in this part showed recent thrombosis. The circular muscle layer was infiltrated by the blood so that the muscle fibres had been separated. The longitudinal layer was intact but much stretched so that it appeared to be very thin. In no part was there any evidence of an inflammatory reaction.

The child's immediate convalescence was complicated by persistent regurgitation of large amounts of heavily

FIG. 1.—Semi-diagrammatic drawing of jejunal specimen resected in Case 1, showing intramural blood clot and compression of the bowel lumen.

bile-stained fluid, and later he continued frequently to vomit copiously similar material. Six weeks after the first operation his readmission to hospital was necessitated by an even more severe bout of vomiting. Laparotomy was performed on the following day. The proximal jejunal stump was found to be dilated and elongated, and it was laterally anastomosed to the efferent loop of the gastro-jejunostomy.

Again episodes of vomiting occurred over the next 15 months and it was firmly thought that these attacks were of psychological origin, for repeated barium investigations showed no significant abnormality. The vomiting, however, demanded further exploration two years from the time of the initial operation. The efferent jejunal loop was traced to the gastro-jejunostomy stoma. The blind end of that loop proximal to the stoma was found to have elongated to about 15 cm. and was dilated. A lateral anastomosis was made between this and the jejunum immediately below the duodeno-jejunal flexure. The gastro-jejunostomy was then undone.

Thereafter recovery was rapid and satisfactory and the boy has remained well.

Case 2. On November 4, 1956, W.K., a boy of 8 years, fell and struck the upper left abdomen across the back of a low chair. He fell asleep shortly afterwards and little was thought of the incident. He went to school on the following day but was sent home as he had been sick three times. He was seen by his doctor who could find no serious abdominal signs. He went to school again on the following day. Repeated vomiting and the complaint of abdominal pain caused him to be sent home again. On the third morning after injury his doctor found him to be tender over the whole abdomen and referred him to hospital. He had been in contact with a case of infective hepatitis. His bowels acted normally before admission.

On examination, he was slightly febrile (99° F.) and the pulse rate was 130 per minute, respiration rate 28 per minute. He did not look ill and was found sitting up comfortably. There was no visible jaundice, the tongue was clean, and the breath odour was a little foul. There was slight tenderness under the left costal margin where it was thought that the edge of the spleen could be felt protruding to one fingerbreadth. It was also thought that the liver margin was palpable and tender. There was no sign of superficial injury.

The provisional diagnosis of an early infective hepatitis or of splenic bruising was made. Five hours later there was more distinct tenderness in the left hypochondrium. Ten hours after admission, there now being acute tenderness and definite guarding in the left hypochondrium with some diffuse tenderness in other parts of the abdomen and absence of bowel sounds previously heard, laparotomy was considered essential.

The abdomen was opened by a left transverse upper incision. On opening the peritoneal cavity, no free blood was immediately evident, but on exploring the left upper quadrant a turgid, congested and oedematous, grossly thickened proximal loop of jejunum was encountered. Close up to the duodeno-jejunal flexure an intramural haematoma, about 3 in. long and surrounding two-thirds of the bowel circumferentially, was present. A small perforation of the serosal coat towards the distal part of the haematoma was oozing dark blood, and in the peritoneal cavity, both above and below the left phrenico-colic ligament and largely below it, was a considerable amount of free and fluid blood. The spleen was of normal size and uninjured. There was considerable oedema in the anterior wall of the lesser sac, especially just below the stomach, but no other injury could be found. Above the jejunal haematoma the normal bowel was insufficient to permit easy anastomosis after resection for it was oedematous and friable. In order to control the bleeding and overcome the intestinal obstruction caused by compression of the gut lumen, the serosa was incised. Adherent and organizing blood clot was with little difficulty evacuated. The underlying muscle coats of the bowel appeared to be healthy but no major bleeding point could be found. The bulk of the haematoma was thus reduced and the thickness of the bowel in this area approximated to the normal. Gaseous bowel content could now be readily expressed proximally through the abnormal segment. The serosal defect was repaired partly by suture and partly by a free omental graft. Intragastric suction was discontinued on the third post-operative day and intravenous infusion on the fourth day. Thereafter recovery was uneventful and a barium meal on the thirteenth day revealed a free flow through the duodenum and jejunum. He was discharged on that day and has remained well.

Discussion

With the relation of the details of these two cases and with the knowledge of one of the two cases already reported in the literature and mentioned briefly above, it is obvious that intramural haematoma of the proximal jejunal loop is no bizarre injury although it is rare. It is a condition which presents several typical features.

It is a child or an adolescent who sustains this injury; it may be only fortuitous that the male alone has been thus afflicted. In him at this age the abdominal musculature has not developed its maximum strength and thickness, the lower rib cage is free and on that account more flexible, and the antero-posterior depth of the abdominal cavity is smaller than in the adult. At the time of impact in the upper left abdomen the musculature is further weakened and caught off guard by the forward flexion of the trunk. It is well known that the fixity of the bowel in this situation, as also in the ileo-caecal region, renders it more vulnerable to injury by sudden and deep violence. The vertical orientation of this loop and its situation to the left and behind the central prominence of the vertebral bodies and the posterior relation of the retroperitoneal musculature have the effect of cushioning the bowel at impact. Similar factors operated in

a case of haematoma of the wall of the ascending colon, although in that case the condition only came to light some months later with organization of the clot and the production of a palpable tumour and a space-filling lesion on examination by a barium enema (Kratzer and Dixon, 1951). Less fixed loops of small bowel are more vulnerable to such injury when they lie transversely and as they cross the anterior prominence of the vertebral bodies. In these circumstances perforation of the affected loop appears to be more probable although, as mentioned above, an acute intramural haematoma may result (Zabin, 1952).

The pathological effects of this injury are not immediate and, as the bleeding into the layers of the bowel wall proceeds, increasing disturbance to bowel function develops. Intraperitoneal bleeding, if it occurs, would appear to be a later effect. If such bleeding were an early feature, it would seem probable that the escape of blood from the bowel wall would limit the degree of stripping of the muscle layers and diminish the compression effect upon the bowel lumen and retard or diminish the resulting intestinal obstruction. This obstruction is not entirely the result of mechanical compression but is also and perhaps even to a major degree the result of the disruption and infiltration of the muscular coats of the bowel wall. Such intramural bleeding has been reported as occurring in the small intestine in association with duplication, ulceration within which may penetrate a small but significant blood vessel (White and Wollenman, 1956). A similar case, presenting with intestinal obstruction, has been encountered personally.

The clinical course after injury presents typical features. After the momentary effects of the blow in the region of the solar plexus, a latent and quiescent period of some hours, and usually of a day or two, ensues. Increasingly severe upper left abdominal pain associated with recurring vomiting follows. Gradually the indeterminate physical signs become more definite. Earlier recognition of the urgent condition seems more probable where there is eventually an associated intraperitoneal leakage of blood.

At laparotomy which, in the circumstances of the typical injury and in the presence of the developing acute abdominal signs, is desirable and probably inevitable, this lesion is encountered in one of the more inaccessible reaches of the abdomen. The lapse of time which has often occurred since injury has permitted the development of a considerable amount of reactionary oedema and an inflammatory response. Resection and reconstitution by anastomosis may appeal as a definitive form of treatment, but in this situation and in these circumstances, these procedures to be safe are difficult. The intramural bleeding which occurs in Henoch's purpura, with the resulting obstructive state, is often successfully countered by conservative means. This suggests that a less radical approach to the present problem is justifiable. That this is so is borne out by the second case reported here and by the other typical case described by Lampert, Goodfellow and Wachowski (1954). Intramural haemorrhage in association with duplication will always necessitate resection.

Summary

The literature concerning traumatic lesions of the intestines caused by non-penetrating blunt blows is reviewed with especial reference to the jejunum and intramural haematoma of its proximal loop.

Two cases of traumatic intramural haematoma of the proximal jejunal loop are described.

The aetiological, pathological and clinical features of the condition are detailed.

The treatment of this and similar lesions is discussed.

I have to thank Mr. J. J. Mason Brown for permission to quote fully the details of Case 1.

REFERENCES

Counseller, V. S. and McCormack, C. J. (1935). *Ann. Surg.*, **102**, 365.
Kratzer, G. L. and Dixon, C. F. (1951). *Proc. Mayo Clin.*, **26**, 18.
Lampert, E. G., Goodfellow, J. G. and Wachowski, T. J. (1954). *Ann. Surg.*, **140**, 768.
Morgagni, J. B. (1761). Epistola, quoted by Poer and Woliver.
Poer, D. H. and Woliver, E. (1942). *J. Amer. med. Ass.*, **118**, 11.
Vance, B. M. (1923). *Arch. Surg. (Chicago)*, **7**, 197.
White, R. J. and Wollenman, O. J. (1956). *Ann. Surg.*, **143**, 720
Zabin, A. (1952). *N.Y. St. J. Med.*, **52**, 93.

HEAD INJURIES IN CHILDHOOD*

BY

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In most respects the mechanisms and effects of head injury in children are the same as in adults, but there are several differences, and these are discussed with particular reference to the 150 children who were seen in the Department of Surgical Neurology, Edinburgh, during the five-year period 1950-54 (Table 1). During this time 450 adults with head injuries were also treated. It is realized that these are selected groups of patients with head injury.

TABLE 1
TOTAL NUMBER OF PATIENTS, 1950-54

Age in Years	Males	Females	Total
0– 1	10	6	16
2– 5	20	14	34
6–12	50	11	61
13–16	31	8	39
	111	39	150

Sixty-one per cent. of the children had mild head injuries, requiring only a brief stay in hospital, they usually had no residual neurological abnormalities and did not require special surgical treatment. The remainder had severe injuries. In the adult series 32% had mild and 68% severe head injuries.

Pathology

In the adult a dynamic head injury is more liable to produce severe displacements of the brain and its blood vessels than is the case in children, where a higher proportion of depressed fractures, and on the whole a lower morbidity and mortality are found (Table 2, Fig. 1). Greater re-organization of nervous function appears to be possible in the child, but babies and young infants have delicate skulls, nervous tissue, and blood vessels, and do not withstand head trauma well. In Table 3 the type of injury is analysed.

Basal fractures of the skull were uncommon in children, but linear, diastatic and in particular compound fractures were frequently seen (Table 2).

TABLE 2
TYPES OF SKULL FRACTURE

Linear	26
Depressed, simple	9
Depressed, compound	52
(1) Involving frontal air sinuses:	
(*a*) Minimal cerebral damage	10
(*b*) Severe cerebral damage	2
(2) Other regions:	
(*a*) Minimal cerebral damage	30
(*b*) Severe cerebral damage	10
Total	87

FIG. 1.—Radiograph showing depressed fracture in left parietal region.

TABLE 3
TYPE AND SEVERITY OF INJURY

	Mild	Severe	Total
Acceleration (including penetrating injuries)	44	25	69
Deceleration	40	23	63
Crush	7	4	11
	91	52	143

Although accurate comparisons between the childhood and adult series is not possible, 35% of the former category had depressed compound fractures, which were present in only 12% of the adults.

* Read at the annual meeting of the British Association of Paediatric Surgeons, Edinburgh, June 6, 1957.

Possibly because of the late formation of the frontal air sinuses (6th-7th year) in children, they were involved less frequently than in adults.

Ingraham and Matson (1954) analysed the records of 1,330 children with head injuries seen during a 13-year period. Twenty-eight per cent. had cerebral concussion, 11% had depressed and 4·5% compound skull fractures. Two per cent. had an extradural haematoma, and 24% subdural haematomas. Regarding the latter, they state that the frequency with which it is found is proportional to the intensity with which it is sought. Although half of their patients with an extradural haematoma were under 2 years of age, this has not been our experience. The adherence of the dura to the skull and its fusion with the fontanelle may partly account for this (Voris, 1950). Seven per cent. of our children had extradural haematomas, 4% subdural haematomas and 6% intracerebral haematomas; the corresponding percentages in the adult series were 4, 13 and 2.

Even a mild head injury in a child who happens to have hydrocephalus can have serious effects, thus a patient with 'arrested' hydrocephalus may show evidence of rapidly increasing intracranial pressure.

Cerebral thrombophlebitis and venous sinus thrombosis account for some of the neurological signs seen in patients with head injuries and appear to be more significant in children than in adults.

Clinical Aspects

Clinical neurological evaluation is often difficult in the young, especially in the first three months of life, and a reliable history and careful, repeated clinical observation are important.

Eleven patients had an extradural haematoma, the ages varied from 4 to 11 years, and on the whole the history was briefer than was obtained in adults and there was often no initial period of unconsciousness. Epilepsy was not a feature. Voris (1950) had no patient below the age of 10 years with an extradural haematoma.

A characteristic syndrome was not found in infants with chronic subdural haematomas, but irritability, restlessness, epilepsy, vomiting, fever, a bulging fontanelle, retinal haemorrhages and drowsiness were sometimes present. The ability of the infant's head to enlarge to accommodate the haematoma probably accounts for the differences in the clinical picture in the child. Bilateral subdural haematomas are more commonly found in children than in adults.

Birth Injuries

In addition to the 150 children under discussion, 64 patients with cerebral birth injuries were treated in the same five-year period. The true incidence and significance of cerebral birth injuries is unknown, but they appear to be common (Anderson, 1952). Of the 64 patients, 33 had epilepsy, 16 amentia and hemiplegia, 11 hydrocephalus and four had chronic subdural haematomas. Much is to be learnt about these sequelae of birth injury, and it is suggested that closer cooperation amongst the various specialists involved is necessary.

Special Methods of Investigation

Skull radiographs are important to demonstrate the size and location of the fragments of a depressed fracture (Fig. 1), and the presence of radio-opaque foreign bodies, otherwise they are of limited value. Three of the 11 patients with an extradural haematoma had no fracture, five had linear and three compound depressed fractures.

Occasionally a slowly progressive intracranial expanding lesion in a child may cause local enlargement and thinning of part of the skull. This was seen in the left temporal bone and middle cranial fossa of a 9-year-old boy, who had a chronic subdural haematoma (Fig. 2).

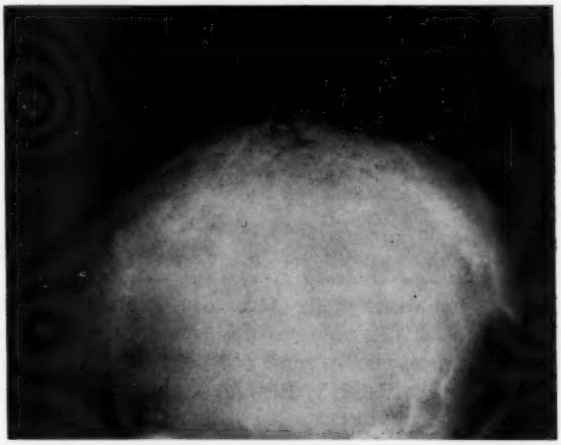

FIG. 2.—Radiograph showing enlargement of left middle cranial fossa with thinning of the skull, due to a chronic subdural haematoma.

Lumbar puncture is of very limited value in diagnosis and in fact may be dangerous in the unconscious or in the restless child. Thus, tentorial impaction may be induced if there is an intracranial haematoma.

In the early stages of a head injury in a child, electro-encephalography has been unhelpful in our experience. Even in the later stages, it may be difficult to interpret the findings in an infant.

Associated Injuries

These usually consisted of fracture of a limb bone (femur in seven cases, tibia in three, humerus in

three, ulna in one, clavicle in four. Two patients had maxillo-facial injuries necessitating special treatment. One patient had a vascular and peripheral nerve injury.

Infection

In one patient a scalp laceration became infected, and in another a brain abscess developed as the result of the penetration of the right frontal lobe by a garden fork.

Sequelae

Twenty-six per cent. of the patients had post-traumatic epilepsy (Table 4). In half there were clinical motor or sensory components. Only five of the children with epilepsy had a compound fracture of the skull with direct cerebral contusion and laceration. Twelve had had no initial period of unconsciousness associated with the head injury. As Livingston (1954) observes, children sustain very many bumps and bruises, and the significance of a head injury in a child in causing epilepsy can be difficult to decide. But on the other hand, 'cryptogenic' epilepsy has a definite stigma, and parents may thus prefer to over-stress the history of a previous head injury. Of 82 children with head injuries studied by Rowbotham, Maciver, Dickson and Bousfield (1954), only four had epilepsy.

Thirteen per cent. of our series of patients had psychological changes (Table 4) and in half of these

TABLE 4
SEQUELAE

Epilepsy	39
Persistent psychological changes ..	20
Dysphasia	12
Other neurological abnormalities ..	27

they persisted. When there has been profound depression of all higher functions from a severe brain injury the early phase of recovery of normal alertness is probably shorter in children than in adults. The next phase, in which there is normal alertness but lack of normal self-control, is commonly more striking in children, but again is usually of shorter duration and less frequently requires prolonged psychiatric care. The late phase, in which there may be full neurological recovery but in which residual unfavourable psychological reactions are still present, is relatively infrequent in children. Compared with adults (25%), the typical 'post-concussional syndrome' was rare in children (6%). Six of the latter were over 15 years of age. Adult attitudes appeared to be important. However, Rowbotham *et al.* (1954) found that 33% of children who had head injuries developed changes in temperament, and eight showed an intellectual injury of some degree. Bakwin (1949) also discusses behaviour disorders in children as a result of cerebral damage.

Recovery from brain injury is probably more rapid and complete the younger the individual, but adequate assessment is always necessary since children are relatively uncomplaining patients, and quite serious disabilities may go unnoticed by ordinary methods of investigation. On leaving hospital they may then either be kept off all schooling for unjustifiably long periods, or else be subjected to educational pressures which are beyond their capacity. This is perhaps particularly the case with language disabilities, in which difficulty in learning to spell and read may persist long after oral speech appears to have recovered. Oral speech indeed may not have been suspected of abnormality, for frank jargon is rare in children and muteness in the early stages of recovery may have been regarded as due to unwillingness rather than to inability to speak.

Dysphasia occurred in 12 of our patients and persisted to an important degree in four. It is interesting that if the brain injury occurred at an early age (before 2 years) and involved the left cerebral hemisphere, several of these patients became left-handed and developed speech normally. Other neurological abnormalities consisted mainly of varying degrees of hemiparesis, and, especially in those with the more severe dynamic head injuries, extrapyramidal signs.

Fatalities

There were 15 deaths (10%), and this number reflects the type of patient that tends to be referred to a neurosurgical department. Nine of these deaths were inevitable, as severe primary or early secondary brain-stem damage was evident when the patient was first seen. One of the other patients, who had an associated fractured femur, died from fat embolism. The most important group were those patients with an extradural haematoma, four of whom died. In each there was delay in instituting treatment.

The fatality rate in the adult series of patients with head injury was two and a half times that of the series in children.

Treatment

If the clinical features or radiological appearances in a patient with a depressed skull fracture suggest brain damage, surgical exploration of the wound is indicated. The depressed bony fragments are elevated and necrotic brain and blood clot removed. A serious contracting scar must be avoided (Penfield and Erickson, 1941).

The brain grows rapidly in the first years of life and therefore intracranial space-occupying lesions must be promptly removed. If not, cerebral atrophy may result, often with important psychological and physical abnormalities (Fig. 3).

Small skull defects in young children recalcify, but

for protective, cosmetic and personal reasons cranioplasty, using tantalum or acrylic, is necessary for large defects. It was carried out in 13 of the series of patients under discussion. In the initial stages of a severe head injury, warmth was previously used to treat shock, but nowadays cooling of these patients has been often found to be life-saving.

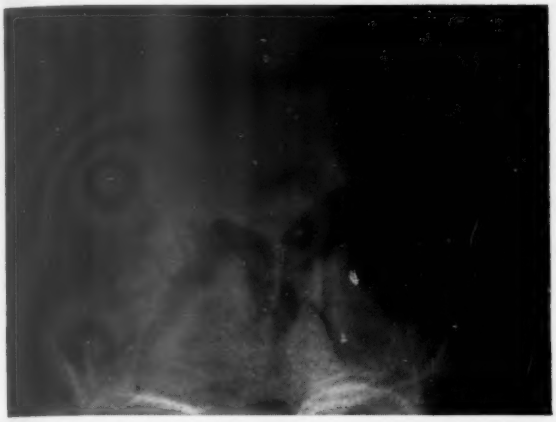

FIG. 3.—Encephalogram demonstrating enlargement of the left lateral ventricle as a result of cerebral atrophy secondary to delayed evacuation of a subdural haematoma.

Less vigorous cooling is necessary in children than is required in adults. Other recent advances in the surgical treatment of certain types of epilepsy—the cause often being a head injury in infancy—include temporal lobectomy and hemispherectomy.

There appears to be no real evidence to suggest that the prophylactic use of anti-epileptic drugs prevents the development of post-traumatic epilepsy in children.

Causes and Prevention of Accidents

There were 56 traffic accidents, seven of the children being cyclists, nine passengers, and 40 pedestrians. Thirty-seven patients fell, and most of the remainder received direct blows to the head by stones, pickaxe, javelin, etc. Children tend to have poor judgment, are impulsive, and the movements of the younger ones are rather incoordinate, and they are therefore susceptible to accidents. There is a striking sex difference (Table 1) in that males predominate in a ratio of 3 to 1.

Many of the accidents occurred because parents permitted young children to play in the street. Education and example are very important in the prevention of accidents to children; however, warnings can be overdone, and the child may develop a 'deaf ear'. The causation and prevention of traffic accidents are fully discussed in 'Medical Aspects of Traffic Accidents' (The Sun Life Building, Montreal, 1955). Dietrich (1954) also discusses the problem.

A few of the patients under discussion appeared to show accident proneness, and, as Langford (1953) points out, this is not quite the same as is found in adults. The children tended to be of the overactive, impulsive type, often with insecure home conditions.

Conclusions and Summary

The main features of head injuries in childhood are discussed, with reference to 150 consecutive patients, and comparisons are made with head injuries in adults. The greater number of male patients was striking (3 : 1). There was a higher percentage of mild head injuries in children (2 : 1), and a correspondingly higher mortality rate in adults (2·5 : 1). Whereas depressed fractures were common in children (3 : 1), basal fractures were infrequent. Hydrocephalic children may be more severely affected by a head injury than normal children. Clinical neurological assessment can be difficult in young children. Greater cooperation of doctors in different specialities may permit of a better understanding of the incidence, significance and management of birth injuries.

Lumbar puncture and electro-encephalography are of limited use in diagnosis. The incidence of post-traumatic epilepsy was 26%; neither obvious cerebral contusion nor an initial unconscious period were necessary for the appearance of epilepsy. Psychological disorders were not uncommon; their diagnosis and significance are discussed. A medical psychologist is an important member of a head injury team. 'Post-concussional syndromes' are rare in children.

Proper treatment of compound fractures of the skull and the timely evacuation of intracranial haematomas are important.

Accident susceptibility, proneness and prevention in relation to head injuries in childhood are discussed.

I wish to acknowledge with gratitude the valuable help given to me by Dr. J. A. L. Naughton, M.C., medical psychologist, in the management of psychological disorders occurring in these patients, and also for his help in the preparation of this paper. I am indebted to Professor N. M. Dott and Mr. F. J Gillingham for kindly allowing me to include certain of their cases in this series.

REFERENCES

Anderson, G. W. (1952). *J. Pediat.*, **40**, 340.
Bakwin, H. (1949). *Ibid.*, **34**, 371.
Dietrich, H. F. (1954). *Pediatric Clinics of North America* [Nov.], p. 759. Philadelphia and London.
Ingraham, F. D. and Matson, D. D. (1954). *Neurosurgery of Infancy and Childhood.* Springfield, Illinois.
Langford, W. S., Gilder, R. Jr., Wilking, V. N., Genn, M. M. and Sherrill, H. H. (1953). *Pediatrics*, **11**, 405.
Livingston, S. (1954). *The Diagnosis and Treatment of Convulsive Disorders in Children.* Springfield, Illinois.
Penfield, W. and Erickson, T. C. (1941). *Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures.* Springfield, Illinois.
Rowbotham, G. F., Maciver, I. N., Dickson, J. and Bousfield, M. D. (1954). *Brit. med. J.*, **1**, 726.
Voris, H. C. (1950). *Arch. Surg.* (*Chicago*), **60**, 906.

INJURIES INVOLVING THE TEETH AND JAWS IN YOUNG CHILDREN*

BY

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The literature relating to fractures of the teeth and facial bones is surprisingly devoid of specific references to such injuries in the young child. With the object of endeavouring to make good this omission from the standard literature, it is intended to discuss some of the general aspects of maxillo-facial injuries in the child from birth to the age of 12 years.

What are the peculiarities of the young child which necessitate especial consideration in so far as treatment is concerned? These are essentially physical and mental. Physically the average child is not prone to serious facial injuries. This is readily borne out by the fact that less than 1% of all facial fractures occur in children of 6 years of age and under (MacLennan, 1956). Kazanjian and Converse (1949), state that 10% of all fractures of the mandible occur in children between the ages of 4 and 11 years, which further serves to indicate that the incidence of such lesions increases with age. Fractures involving the maxillary region account for less than 0·25% of those cases which have been dealt with by the author. To what can these low figures be attributed?

(*a*) The bony scaffold of the face in the young child is relatively elastic and in health, allied to the configuration of the anatomical structures concerned, does appear to possess a resistance to fractures which is not present in the adult to the same extent.

(*b*) Children are not exposed to as many of the hazards which predispose to fractures of the facial bones in adults.

Mentally, the average child who has been involved in an accident is not at all kindly disposed to cooperate in the course of his or her treatment. The belief that all children are fundamentally cooperative is an erroneous one. While it is undoubtedly true to state that time spent in gaining the confidence of a child will pay handsome dividends, it is only fair to observe that the very nature of the treatment required frequently places a premium on speed and efficiency if worthwhile results are to be obtained. Definitive treatment should therefore be undertaken so as to ensure that there are a minimum number of sessions between the child and the surgeon. The value of premedication and of anaesthesia should never be overlooked. Every effort should be made to provide fixation apparatus which is simple in construction, reliable, self-retaining and easy to keep clean. As in the treatment of all injuries involving the oral cavity a high degree of oral hygiene is essential throughout.

Before proceeding further it is intended to enumerate several details in respect of the deciduous and permanent dentitions which are related directly or indirectly to planning treatment in fractures of the facial bones in children.

(1) The complete deciduous dentition numbers 20, while that of the permanent dentition numbers 32.

(2) Every tooth consists of enamel, cementum, dentine and pulp, the latter of which is the vital structure most prone to irreparable damage following injury.

(3) A tooth with an open apex to the pulp canal has a better prognosis after trauma than that in which the apex has closed.

(4) The first permanent or 6-year-old molar tooth erupts immediately behind the second deciduous molar tooth.

(5) The shape of the crowns of the deciduous teeth is such that they tend to be widest at the cervical margin compared with teeth of the permanent dentition which constrict at the cervical margin: this precludes the use of the former for control with dental wiring or cast metal cap splint techniques, an observation which is also applicable to children with a mixed dentition of partially erupted permanent teeth and deciduous teeth with partially resorbed roots.

(6) In the deciduous and mixed dentitions the dental follicles of the still unerupted teeth, allied to the presence of secondary centres of ossification in bone,

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

contraindicate the use of transosseous wiring as a method of fixation of fractures.

What are the most common causes of fractures of the teeth and facial bones in young children? They are: (*a*) A fall from a height; (*b*) a vehicular accident, child knocked over by a car, lorry, bus, etc., or fall from a bicycle; (*c*) accidental blow at sport, e.g., a blow from a hockey stick, a collision at soccer, a kick at rugby football.

Having alluded to the most common causes of fractures in children, it is proposed to enumerate the sites of these fractures in order of frequency omitting those of the nasal bones and skull, which it is not intended to deal with in this paper. They are: Fractures of teeth; subluxation of a tooth or teeth plus a fracture of the alveolus; dislocation of a tooth or teeth plus a fracture of the alveolus; fracture of the mandible condyloid process, of the body of the mandible, of the body of the mandible plus fracture of the condyloid processes; fracture of the zygomatic arch and/or zygomatic (malar) bone; fracture of maxillae.

Treatment of fractures of the facial bones can be considered under two headings, general and local. The general treatment in serious cases must be given precedence over the more specific local treatment. It should never be forgotten that the most perfect fixation and control of the local fractured fragments is of little avail if the child is lying in the mortuary. When the case is first seen the immediate attention should be directed towards the 'four controls', namely, control of respirations, control of haemorrhage, control of shock and control of the fractured fragments.

The routine use of antibiotics is to be deplored. There is, however, one definite indication for their use, namely, in those cases in which involvement of the meninges is suspected, when the patient should immediately be placed on penicillin and sulphadiazine or sulphamethazine to guard against the possibility of meningitis. In other instances, antibiotics should usually be withheld unless there is, for example, a sudden rise in temperature or infection of the wound. In the latter a culture and/or antibiotic sensitivity test should be completed where possible.

The aim in treatment of all maxillo-facial injuries is to achieve reduction, immobilization and fixation of the fractured fragments in as near to the original anatomical position as possible. The following methods of local treatment are outlined, not because they are the only ones but rather because they serve to indicate some of the ways in which fractures of the facial bones can be dealt with, and in particular to draw attention to the fact that many teeth can be conserved if the correct treatment plan is followed with a minimum of delay. Many teeth have been needlessly sacrificed in the past either because of lack of facilities or lack of knowledge; neither is a valid excuse for producing abnormalities in a child which will persist, on occasion in an aggravated form, into adult life.

In fractures of teeth, the type of dentition influences the treatment, as also does the extent of tooth involvement. In the deciduous dentition the tooth or teeth concerned are usually extracted and a space retainer inserted where necessary. In the permanent dentition every effort should be made to retain the teeth (Fig. 1). There are essentially four types of fracture in the teeth of the permanent dentition: (1) Fracture of the crown of the tooth not involving the pulp canal; (2) fracture of the crown of the tooth involving the pulp canal, the apex of which is open; (3) fracture of the crown of the tooth involving the pulp canal, the apex of which is closed; (4) fracture of the root of the tooth.

Fractures of the crown may necessitate pulp capping, pulpotomy or even pulpectomy followed by insertion of a root filling before the aesthetic conservation of the fractured tooth. With fractures of

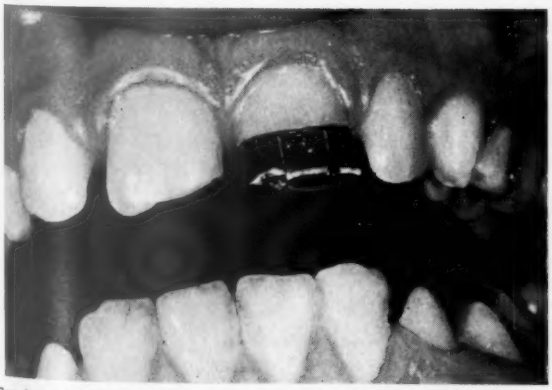

FIG. 1.—Stainless steel lined cap to protect tooth with fractured crown.

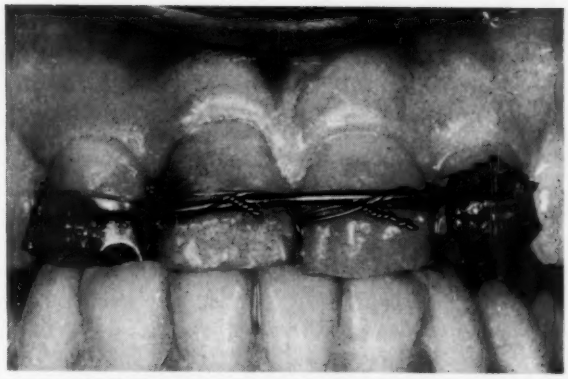

FIG. 2.—Modified arch bar to splint a tooth with a fractured root.

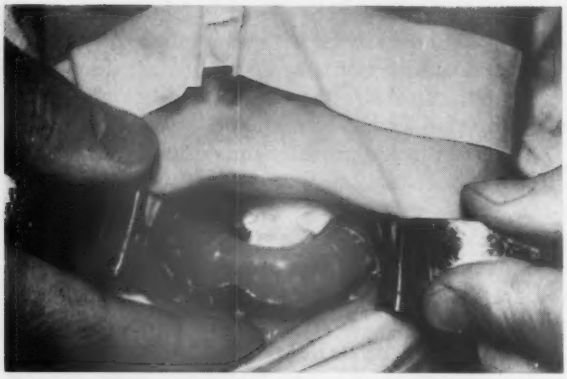

FIG. 3.—Acrylic overlay splint with circumferential wires to control a fracture of the mandible.

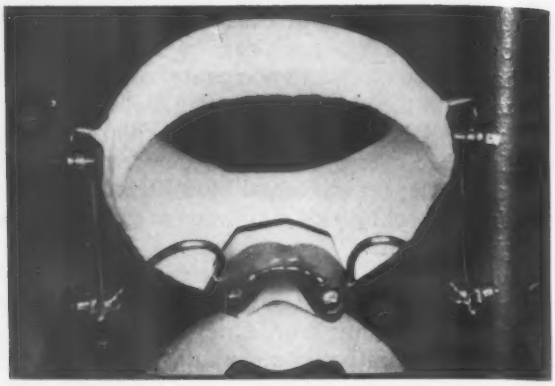

FIG. 4.—Type of acrylic splint with lateral tubes and plaster of paris headcap for control of fracture of the maxillae.

the root it is essential to splint the tooth or teeth concerned and endeavour to keep occlusal stresses and strains from them in order to avoid further trauma (Fig. 2). With fractures of the alveolus the bone should be manipulated as soon as possible, teeth which cannot be retained extracted, and the mucoperiosteum carefully sutured, while teeth requiring support should be splinted. In fractures of the mandible, if the condyloid process alone is fractured, a supporting bandage for 10 to 12 days will suffice. MacGregor and Fordyce (1957) state that such fractures do in fact unite without any specific methods of control and point out that subsequent maldevelopment is not a complication. When the body of the mandible is involved the fragments should be fixed for a period of three to four weeks (Fig. 3), and can very simply and efficiently be effected by means of an acrylic overlay splint lined with black guttapercha and wired around the mandible (circumferential wiring). The Gillies temporal operation is a simple method for dealing with fractures of the zygomatic arch and/or zygomatic bone. More extensive procedures should not be embarked upon unless there is a definite indication for so doing.

Lastly there is the treatment of the child with a fracture of the maxilla to consider. Fortunately, even the young child tolerates a plaster of paris headcap extremely well, and this can be utilized in conjunction with a modified Kingsley-type splint with lateral tubes for stability (Fig. 4). After the splints have been removed it should be appreciated that any minor discrepancy in the occlusion of the teeth will readily correct itself spontaneously. On completion of treatment every child should be encouraged to acquire the habit, if this has not already been established, of attending the dental surgeon regularly. In this way any necessary conservative and orthodontic correction can be carried out.

Summary

Various aspects of fractures involving the teeth and facial bones of the young child have been discussed including causation, sites and the general principles of treatment employed. The importance of preservation of teeth and of realignment of the fractured fragments as soon as possible has been emphasized.

I am indebted to Mr. J. Ball, Edinburgh Dental Hospital, for Figs 1 and 2, and Mr. D. Franklin, photographer, Bangour General Hospital, for the illustrations.

REFERENCES

Kazanjian, V. H. and Converse, J. M. (1949). *The Surgical Treatment of Facial Injuries*, p. 100. Baltimore.
MacGregor, A. B. and Fordyce, G. L. (1957). *Brit. dent. J.*, **102**, 351.
MacLennan, W. Donald (1956). *Brit. J. plast. Surg.*, **9**, 125.

THE PREVENTION OF ACCIDENTS IN CHILDHOOD IN SWEDEN*

BY

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The problem of accidents in childhood has aroused considerable interest in Sweden during the last few years. The impressive figures on accidental deaths in childhood provided by mortality statistics brought about, in 1954, the constitution of a Joint Committee for the Prevention of Childhood Accidents, including representatives of a number of interested organizations (the Red Cross, Save the Children Fund, National Society for Road Safety, Swedish Fire Protection Association, the Association for Promoting Elementary Swimming, Board of Health, Board of Education, Association of Nurses, women's organizations, etc.). Two medical advisers were attached to this Committee, one a paediatrician with a special interest in social paediatrics (Dr. R. Berfenstam, Upsala) and the other a paediatric surgeon (Dr. Th. Ehrenpreis).

The principal aims of this Committee have been to incite studies of the problem, to promote safety measures and to inform the public.

Accident Studies

Mortality statistics show a remarkable decrease in infant and childhood mortality during the last decades. The various causes of death do, however, play a very different part in this decrease. The most spectacular improvement has been attained within the group of infectious diseases, whereas accidental death has diminished only slightly. This has resulted in a gradual increase in the proportion of accidental deaths in childhood as shown in Fig. 1 prepared from Swedish mortality statistics.

Except for the facts provided by mortality statistics, we know very little about the epidemiology of accidents in childhood. Clinical experience seems to indicate that although there is no actual increase in accident mortality, there is probably a definite increase in accident morbidity. Another experience that emerges from daily work with injured children is that accidents to a large extent are preventable.

It was keenly felt that a better knowledge of accident morbidity in childhood would be a prerequisite to all kinds of preventive measures. As

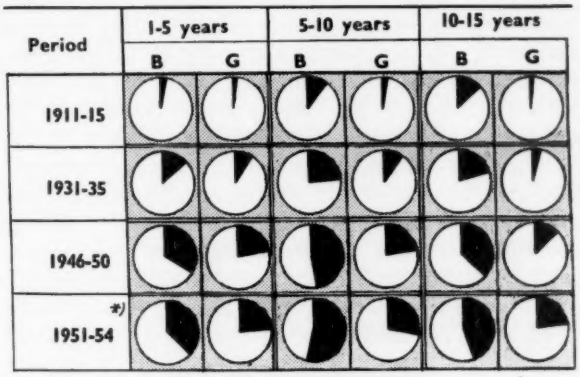

FIG. 1.—B=boys. G=girls.

a first step an enquiry was made (Berfenstam, Ehrenpreis, Ekström, Garsten and Myrin, 1957) into all accidents in children (0-14 years) treated as in- or out-patients in all the hospitals of Stockholm during one year (1955). The number of children aged 0-14 years old in Stockholm is 227,000. The number of accidents among these children throughout the year 1955 was 24,466 and the number of deaths 29. Thus every tenth child had an accident during the year, which is a much higher morbidity rate than we had expected to find. It had been estimated earlier that every accidental death would correspond to between 100 and 400 non-fatal injuries. This investigation has given us the proportion as 1 : 840.

A rough estimate of the degree of severity of the injuries has been made according to whether the child was an in- or out-patient. Only 1,539 cases (6·4%) were treated as in-patients.

Sex distribution showed a definite male predominance but not nearly as marked as for accidental deaths.

As for the time and place of the accidents, some interesting facts emerged. The hourly distribution shows a relatively high level between 10 a.m. and 8 p.m. with one small peak between 11 a.m. and noon and a definite maximum between 3 and 6 p.m.

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

These are in Stockholm the hours just before luncheon and dinner time, respectively. In all probability the children are left alone during these hours more than at other times. Further it may be assumed that they are hungry and more irritable before meals than after, especially at dinner time. The afternoon peak is well known from earlier studies on industrial accidents. The distribution among week days is fairly even from Monday to Saturday, Sundays and holidays showing a decrease of about 20%. A special study of road accidents shows the same daily distribution, which does not agree with earlier experience from studies on road accidents. This might be due to the fact that motor vehicles were involved in only 30% of our road accidents. In 66 %of the road accidents, bicycles only were involved. The different months of the year show variations mainly in the accident pattern. The distribution of the various kinds of accidents and the various causes of accidental deaths do not correspond at all. The principal types of accidents were home accidents (40%), school accidents (28%) and road accidents (10%); the main causes of death were road accidents (34%), drowning (31%) and suffocation (10%). Home accidents were responsible for 0·35% of the deaths only and school accidents had no mortality at all.

A cautious estimate of annual community expenditure for medical care alone caused by childhood accidents gives a total of about 1·25 million swedish crowns in Stockholm with a population of about 1 million (227,000 children). To this we have to add family expenses for doctor's fees, transportation, loss of income, etc. Finally, the disaster produced by permanent disability or death is quite immeasurable. The magnitude of the problem is evident. A careful analysis of the information provided by this study may help us towards a future reduction of accident morbidity and prevention of its most serious results.

Safety Measures

A great number of things can be done to reduce the dangers in childhood. Most of these dangers are (in Sweden) localized to the roads, the waters and the homes.

Road accidents constitute one of the major problems of today in all civilized countries. Attempts to rouse public opinion are in progress everywhere and may prove to be our most important safety measure in this field. Others include sensible traffic regulations, supervision of small children and systematic training of pre-school and school children. More specific protection is offered by safety belts, special seats for baby passengers in cars and on bicycles, lockable car doors, etc. This field is in Sweden well covered by our National Society for Road Safety.

The principal safeguard against drowning is promotion of swimming ability, especially through the schools. During the last 10 years there has been a marked increase in the proportion of school children who know how to swim. This has resulted in a marked decrease in mortality from drowning. For the small children a very important thing is to have wells safely covered and closed.

The home at present seems to be the most dangerous place for our children, 40% of their accidents being home accidents. Two types of home accident are especially worthy of preventive efforts: burns and poisoning. The open fire is not nearly as important a cause of disaster in Sweden as in Great Britain: central heating actually seems to be a very good safety measure. Electric burns are very nasty. They are due to faulty electric equipment or to meddling with the electric outlets, especially with scissors or nails. A Swedish electrical firm (Joel Olsson, Stockholm) has devised an outlet, where the plug holes are covered by a valve, which opens for the appropriate 2-pin plug only after introducing it into the upper part of the receiver and bringing the valve downwards. The real plug-holes are then entered through the lower part of the receiver (Fig. 2).

FIG. 2.

The obvious safeguard against accidental poisoning is to keep every potential poison under lock and key. Some of these preparations may, however, be needed several times every day, especially cleaning agents, etc., and it would be very inconvenient to have them locked away. A rural policeman in southern Sweden has constructed a special safety catch for the cupboard door latch requiring two combined manœuvres before it opens. Experience has shown that toddlers may be very ingenious but they cannot do combined manœuvres, so this simple device is quite efficient.

The same principle has been used by a young Swedish paediatrician in devising a safety bottle-cap. It needs both inward pressure and twisting to open (Fig. 3a); if only unscrewed nothing happens (Fig. 3b). This safety cap ('nixi') (A. B. Termator, Stockholm) is available for all common sizes of bottlenecks and pill-boxes and costs very little.

Informing the Public

Our present knowledge of childhood accidents, however incomplete it may be, gives us more than sufficient cause for rousing public opinion. Every possible means should be used. The Swedish press, radio and television have been very cooperative. Besides these ordinary channels, we have been working out some special schemes. For many years we have had well-organized child welfare centres, where practically every infant is checked. Elementary information on the dangers in childhood and appropriate safety measures are now included in their programmes.

An exhibition called the 'Dangerous World of Childhood' has been circulating for two years now through most of our major towns. Introductory lectures have been given by local paediatricians and surgeons. A popular booklet with the same title, besides serving as a programme to the exhibition, has been distributed to all mothers visiting the child welfare centres and has also been available through the bookstalls.

A series of posters is at present being displayed by the well-known surgical instrument makers, Stille-Werner, in cooperation with our Joint Committee.

Several films have been produced, among others a very good one on road accidents, 'To Kill a Child'. This film was awarded a prize at the Edinburgh Festival a few years ago and has recently been shown on British television.

Time only can tell to what extent our preventive efforts will be effective. It may sound paradoxical, but we do not expect and we do not even aim towards a material reduction of the total number of accidents. As stated before, the morbidity study in Stockholm 1955 showed that only 6·4% of the accidents caused more or less serious injuries. These injuries, and especially the potential causes of permanent disability or death, are the ones we are striving to prevent. Even a very good result within this limited scope would only slightly reduce the total number of accidents.

FIG. 3A.

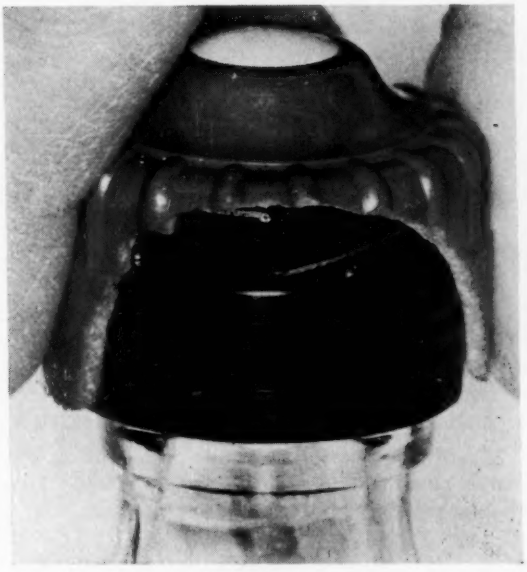

FIG. 3B.

A further increase in our present mortality : morbidity ratio of 1 : 840 would thus seem to be our ideal reward.

One may well ask if this kind of work is within the scope of a paediatric surgeon. I would say definitely yes, and the reasons are two. First, any paediatric surgeon who has to treat a large number of injured children will soon realize that treatment of the individual case is not enough. These injuries repeat themselves in a monotonous way year in year out, and even the most successful treatment of the individual case leaves behind an apprehensive feeling of dissatisfaction. It would obviously be much better to prevent unnecessary accidents than to treat severely injured children. Most serious accidents are unnecessary and ought to be preventable.

The second reason is that people who know the practical side of the problem should engage in this work in order to direct protective measures where they are most needed, even though accident prevention to a large extent may be part of social medicine. As most of childhood accidents are surgical cases there seems to be no person more fitted for this work than the paediatric surgeon.

REFERENCE

Berfenstam, R., Ehrenpreis, T., Ekström, G., Garsten, P. and Myrin, S. O. (1957). *Svenska LäkT.*, **54**, 1950.

COMMUNITY ASPECTS OF TRAUMA IN CHILDHOOD*

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I want to present this issue as forcefully as possible by saying that accidental injury is now the most important public health problem of the childhood and adolescent years. For example, accidental deaths from the age of 5 onwards into early middle life now account for about 20% to 40% of all deaths at these ages.

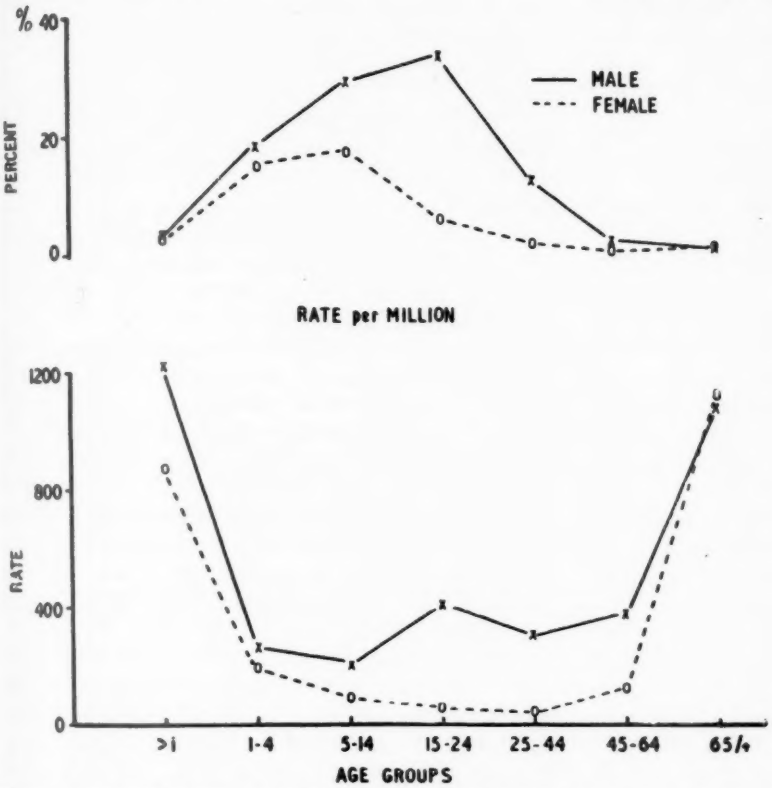

FIGURE.—Fatal accident rates per million and proportion per cent. of all caused, by sex and age in England and Wales in 1950.

This situation is true for all of the so-called advanced countries today. A recent World Health Organization publication on accidents in childhood shows that anything from 25% to 37% of all deaths at ages 1-19 are due to violence (World Health Organization, 1957). It is not that deaths from violence are actually increasing at these ages. They are in fact declining. But other causes of death to the young have been so sharply reduced that accidents emerge starkly as our number one problem today. The great epidemic of accidents is made up of a series of lesser epidemics. These wax and wane as a cause of death. An obvious example of a cause which has been on the increase is accidents on the road. On the other hand, deaths from burns and scalds have been very considerably reduced over a period of time. But undoubtedly a great part of this reduction has been due to better treatment. How far there has been a reduction in burning accidents we just do not know. Presumably there must have been some reduction since the fall in mortality began before modern advances in treatment.

Within the age of youth the amount of risk and the kind of risk changes. Mortality is at its highest in the young child, although reported deaths from violence in infancy include many from suffocation which are only doubtfully to be attributed to mechanical causes.

In a survey dealing with the incidence of accidents in the young child, it was found that the risk of injury is small before the child can sit up, but increases when he sits, and reaches a peak when he can walk and is unsteady on his feet (Rowntree, 1950).

As the child becomes mobile while still uninformed of danger, new hazards beset it in and around the home, which is its world at this stage. These are not only the dangers of fire and water; already at an early age the road begins to take its toll. For

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

example, a study has been made of accidents which occur when a stationary vehicle moves off. In a recent two-year period 160 deaths of this kind occurred in children under 9, 126 of them to children under 4. These grim accidents were mostly concerned with local delivery vehicles at or near the home of the victim (Garwood, 1956).

There has been a substantial reduction in accidental death rates among very young children because of the reduced mortality from drowning and from burns and scalds, whereas with school children and adolescents road accidents have effectively counterbalanced reductions elsewhere. With advancing school age the child ventures farther from home and the bicycle comes into prominence as a fatal instrument. The trend continues into adolescence and mortality rates increase as compared with school age. Other instruments of destruction, such as the motor cycle, appear on the scene, and adventure and sport take their toll (Glanville, 1954).

So far I have been considering the effects of accidents mainly in terms of mortality. But for every death there is some unknown but considerable number of accidents leading to pain, loss of time at school and work, and sometimes to permanent disability.

Valuable evidence has come from a study made by Lee (1955) of the records of boys coming up before National Service Boards. From these records he calculated the proportion who had had accidents in their lives of varying degrees of severity. He also estimated from the Registrar-General's mortality rates for accidents how many boys were, so to speak, missing from the group because of earlier death due to violence. He estimated that among this group of 18-year-old boys seven per 1,000 were missing through death, 10 per 1,000 were excluded as unfit for National Service because of disability left behind by past accidents, 16 per 1,000 were enlisted but put into low medical categories due to disabilities of the same kind, and 89 per 1,000 showed a record of an accident at least of the severity of a fracture without any residual disability. (This last figure is certainly an under-estimation.) This is a record of pretty considerable damage. Accidents were found to be much the commonest cause of orthopaedic disability leading to rejection for National Service. An estimate was made of the comparative damage done by accidents and poliomyelitis to a hypothetical group of 5,000 male babies by the time the eighteenth anniversary of birth is reached. Of these 5,000, one would have died of poliomyelitis as against 33 deaths due to accidents, and 12 would have been so disabled by polio as to be unfit for National Service as compared with 42 from accidents. Incidentally, there seemed, from the National Service Board records, to be evidence that some of the young men disabled by accidents had been inadequately rehabilitated after them and unwisely placed so far as their jobs were concerned.

More than other conditions accidental injuries leave behind the feeling that they should not happen. Yet because human behaviour is so difficult to change and control, effective preventive policies are difficult to develop.

Prevention may be thought of at three levels: (1) Impersonal environmental control: at this level improved neighbourhood planning and road design could do a great deal to keep children off the road. Yet as a nation we seem as impotent to make the major environmental changes necessary as we appeared to be a hundred years ago in the field of sanitary control. Better standards of housing and house design can diminish risks within the home, and Scotland with its unenviable record of overcrowding is still virtually a barbaric country in this respect.

(2) Control of the personal environment, by which phrase I mean the equipment we use in everyday life, and here improvement could be achieved quickly if we really want it. The twin destroyers of girls, the open fire and the inflammable dress, could be brought under control within a year or two if we were determined. Our record in this respect is much worse than other European countries which heat their houses in a more sensible fashion (World Health Organization, 1957). In fact child death and mutilation by fire is an old British custom no less cruel than the Hindu tradition of suttee. However, it looks as though our shameful complacency is shaken at last. The 1952 Heating Appliances (Fireguards) Act, and now the proposal to designate and mark safe fabrics, are steps in the right direction. But resistance to change remains deeprooted, as Wallace (personal communication) has found in his efforts to interest manufacturers in safer designs for teapots and other household utensils responsible for scalding. There is a really encouraging movement towards greater safety in car design. The voluntary movement to encourage bicycle riding efficiency tests for children is doing useful work too; but should such tests not now be compulsory?

(3) Control of personal behaviour: this remains much the most important and yet difficult field for preventive work. I am sure that the child health and education services have already achieved a good deal in teaching children and those who look after

them to be more safety minded. But there is still a tremendous need for well-planned, well-sustained, continuous, patient work. Perhaps as a profession we should take the lead in sponsoring a campaign to infiltrate television and radio subtly, so that continually through the ordinary programmes the public are educated in simple known measures of accident prevention. We know enough to do much already, but there are many things about which we need to know more. We need to know more about how to arouse and maintain interest in this subject. We need to know more about the families and children who are particularly susceptible to accidents; who are the accident-prone children and parents. Douglas and Blomfield found that children experiencing more than one accident in his child health survey (1950) seemed to be larger and probably more active than the rest; they were either more intelligent or more stupid than average. It has been suggested that children involved as pedestrians in road accidents come more often than would be expected by chance from careless and neglectful families. We need more information about the children at greatest risk of accidental injury so that we can direct special efforts to educate them and their guardians.

We need to know more about the incidence of accidents in our own areas, to see the epidemic patterns of accidents, so that we can relate policies to the local situation. We need to know more about what happens to the injured after the accident has happened in terms of first aid, duration of hospital treatment, amount of time lost from school and work, rehabilitation and the amount of residual disability.

Dr. Seiler, the Medical Officer of Health for Edinburgh, has done pioneer work in Edinburgh in studying home accidents (Seiler, 1956, 1957; Seiler and Ramsay, 1954). And recently, motivated by Mr. A. B. Wallace and supported by Sir James Learmonth and Professor John Bruce, the surgeons of Edinburgh have set in motion a survey of all accidental injuries treated as in-patients in Edinburgh and a sample of those coming to out-patient departments. This survey began on April 1, 1957, and it is to last for one year. From this we hope that a picture will emerge which will be helpful in planning arrangements for prevention and medical care.

References

Douglas, J. W. B. and Blomfield, J. M. *Children Under Five.* London. To be published early in 1958.

Garwood, F. (1956). *Some Applications of Statistics in Road Safety Research.* Manchester Statistical Society, March 14.

Glanville, W. H. (1954). *J. roy. Soc. Arts*, **102**, 496.

Lee, J. A. H. (1955). A Study of the Findings of the Medical Boards who examine Young Men called for National Service. M.D. Thesis, University of Edinburgh.

Rowntree, G. (1950). *J. Hyg.* (*Lond.*), **48**, 323.

Seiler, H. E. (1957). *Med. Press*, **237**, 458.

—— and Ramsay, C. B. (1954). *Practitioner*, **172**, 628.

World Health Organization (1957). 'Accidents in Childhood: Facts as a Basis for Prevention.' Wld Hlth Org. techn. Rep. Ser., No. 118. Geneva.

THE RESUSCITATION OF BURNED CHILDREN*

BY

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Burns and scalds remain all too common injuries among children in this country. In any large series of burns in children two major groups are discernible: first the toddler of either sex who is particularly subject to scalds from hot water or tea; secondly, the 5-to-8-year-old, usually a girl, whose clothes catch fire from a naked flame. While the majority of these injuries fall into the 'minor' or 'moderate' categories, each year sees an appreciable number of children admitted with major burns. In the most severe cases, survival for a week or two may represent our present therapeutic limit. Many others will spend long weeks or months in hospital, to emerge once more with an intact skin covering after what can only have been, for a young child, an emotional and physical ordeal. If the coping stone of ultimate recovery is to be reached the foundations must be truly laid, and it is this early fundamental care that forms the subject matter of this presentation.

Burns Shock

Pathology. Rational therapy stems from an understanding of the pathological processes at work. The application of heat to a cutaneous surface damages or destroys the integument and the underlying vascular network. The permeability of the capillary wall is increased, or coagulation *in situ* of the capillary and its contents may result where the heat source is intense or its action prolonged. Through these damaged capillary linings a plasma-like fluid passes out into the extravascular space. The avenues of return to the bloodstream cannot cope with this flood and the fluid accumulates in and around the involved parts of the body. This process begins shortly after injury, is maximal in the first six to 12 hours, slowly diminishes up to 36 hours, and the oedema fluid is thereafter gradually reabsorbed. The protein content of this fluid is commonly of the order of 5 g.% and its electrolyte pattern is that of plasma. In deeper burns, where the vascular damage is greatest, red cells are destroyed either immediately at the site of injury or by lysis of damaged erythrocytes in the reticulo-endothelial system.

Physiology. The protein-rich transudate acts like a leech upon the general circulating plasma volume. The larger the area of the body burned the greater will be the shift from the intravascular compartment to the interstitial space, and to the exterior through the burned surface. The reduction in plasma volume is thus directly related to the size of the burn wound. In children, a critical area can be roughly defined. Should the surface area involved exceed this, then the body's compensatory mechanisms, supplemented by oral fluids, are unable to maintain an adequate circulating volume and the clinical picture of oligaemic shock develops. This 'critical' area ranges from 8% of the body surface in the infant, up to 15% in the 12-year-old child. These figures are lowered by such additional factors as long journeys to hospital, careless or prolonged handling of the patient, or any coexisting illness.

Treatment

The aim of treatment must be to maintain, or restore, the circulating volume within, or close to, normal limits. If oligaemic shock is apparent on admission urgent intravenous therapy is imperative. Should the circulation be found adequate a more detailed assessment of the size of the injury is called for. In this latter group some will be found to have sustained a burn above the critical area, and intravenous therapy should be started to prevent the onset of shock.

Type of Fluid. Plasma or a plasma expander forms the basis of therapy. Reconstituted dried plasma has a protein concentration of approximately 5 g.%, closely comparable to the oedema fluid which it replaces. In extensive full-thickness burns, red cell destruction may diminish the red cell volume by 10 to 20%, and early replacement of this deficit by whole blood transfusion is both rational and rewarding (Raker and Rovit, 1954).

Rate of Administration. During the early hours after injury, when the fluid loss is rapid, replacement

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

must keep pace. The necessary rate of infusion slowly declines from this peak until, towards the end of the second 24 hours, no further colloid infusion will be found necessary. Should infusion be delayed by a lapse of several hours, a really fast rate of replacement must be obtained. For this purpose the veins of the upper extremity are superior to the more customary internal saphenous vein, and a polythene cannula provides the most reliable channel.

Volume of Infusion. No hard and fast figures can or should be given as to the volume of plasma necessary in any one case. The amount must vary according to the size of the patient and the extent of surface burned. The former is gauged by weighing on admission, the latter by reference to surface area charts (Lund and Browder, 1944). A rough estimate may be made that, throughout the whole shock period, up to 3 ml. of colloid solution may be required for each kilogram of body weight and each 1% of surface area burned. One half of this amount may be infused in the first 12 hours after injury. Oral fluids are only allowed when the circulatory state is satisfactory. Such fluids are given as sweetened water or tea, in amounts of from 30 to 60 ml. per hour according to the age of the child. Thirst is not an indication for increasing water intake and an excess water load after a major injury carries its own risk in view of the brake on renal water excretion exerted by the posterior pituitary gland.

Assessment of Response to Therapy

The most valuable test of the response to treatment is a careful comprehensive examination of the patient, performed by an experienced clinician at frequent intervals. In the treatment of extensive burns it is neither advisable nor feasible to lay down a proposed schedule of intravenous fluids for more than an hour or two in advance. The response to treatment is satisfactory when the child is warm, pink and quiet, possesses a normal peripheral capillary return and venous filling, has a firm, stable pulse and a systolic blood pressure of 100 mm. of mercury or more. Where shock is well controlled the child should not vomit unless a meal has been eaten just before the injury.

Valuable confirmation of clinical judgment is obtained from hourly estimations of the urinary output, obtained with the aid of an indwelling urethral catheter. In the first 24 hours urine volumes of not less than 8 ml. per hour in the infant, and not less than 20 ml. per hour in the 12-year-old child are considered adequate. A fall in the urine output is often one of the earliest signs that the infusion is not keeping pace with the loss from the circulation.

Serial estimations of the peripheral haemoglobin and haematocrit suffer from two main disadvantages; representing, as they do, a ratio, these tests are difficult to interpret where there has been much red cell loss, as in deep burns, or where whole blood has been given; moreover, alterations in their values, such as a rise in haemoglobin concentration, represent a change that has already occurred, an existing deficit, with the result that treatment based on these findings must lag at least one step behind the changing situation.

Renal Damage

In many extensive deep burns a temporary pink discoloration of the plasma will be found, if looked for, in the first hour or two after injury. The pigment responsible is methaemoglobin derived from destroyed red cells. Haemoglobinuria, clearly apparent to the naked eye as a chocolate-brown discoloration of the urine, will follow not infrequently. Where kidney function is normal large quantities of pigment can be successfully excreted. In the severe burn, however, two factors predispose towards renal damage from pigment; first, low renal blood flow and, therefore, hypoxia of the tubules, and, secondly, the maximal concentration occurring in the tubules under posterior pituitary influence. Under the combined weight of these adverse factors renal failure with oliguria or anuria then becomes established, the process being similar to the renal damage of the 'crush syndrome'.

In all deep burns of over 20% surface area, an indwelling urethral catheter should be utilized to give early warning of the appearance of pigment. Established shock must be treated with great urgency and an adequate circulating volume restored in the shortest possible time. This alone, by improving renal oxygenation, may be all the help that the kidneys require. In most cases, however, further measures are needed. The promotion of a diuresis will lower the concentration of pigment in the tubules, and thus allow the kidneys to clear themselves. Such a diuresis can only be produced in the post-traumatic phase by the addition to the glomerular filtrate of a substance which passes along the nephron unchanged and unabsorbed, carrying an additional volume of water with it. For this purpose both 'plasmosan' (poly-vinyl-pyrrolidone) and 15% 'mannitol' have been found effective. In any case showing heavily pigmented urine and a declining urinary output, in spite of restoration of an adequate circulation, 8 ml. of 'plasmosan' or 1 g. of 'mannitol' per kilogram of body weight should be given intravenously over 10 to 15 minutes. Where treatment has been prompt a rapid response can be

expected. The urine output climbs sharply and serial specimens show progressive disappearance of pigment (Dudley, Batchelor and Sutherland, 1957).

Local Care

The treatment of the burned surface is beyond the scope of this short paper but reference must be made to the necessity for careful timing of such treatment. No definitive local care is permissible until the circulation has been stabilized at a satisfactory level for at least an hour. Failure to observe this simple rule will predispose to the reappearance or intensification of shock.

In conclusion, it should be stressed that there is no area of surface involvement too great to permit successful resuscitation. In the absence of respiratory tract injury early, vigorous and meticulous treatment will ensure the survival of the child beyond the phase of oligaemic shock.

References

Dudley, H. A. F., Batchelor, A. D. R. and Sutherland, A. B. (1957). *Brit. J. Plast. Surg.*, **9**, 279.

Lund, C. C. and Browder, N. C. (1944). *Surg. Gynec. Obstet.*, **79**, 352.

Raker, J. W. and Rovit, R. L. (1954). *Ibid.*, **98**, 169.

SPONTANEOUS DISLOCATION OF THE CERVICAL SPINE IN CHILDHOOD

BY

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This paper is based on a series of 10 cases of spontaneous dislocation of the cervical spine. In the 10-year period, 1946 to 1955, nine cases were seen out of a total of 19,270 surgical admissions. A further case was seen in 1956.

I.H., a boy aged 3½ years, was admitted with the history that 10 days previously he had been playing with his uncle who had been tossing him into the air and catching him again. One hour later the child complained of pain in his neck and of earache. His mother noticed that he was holding his neck rigidly and so put him to bed. The next day the family doctor saw him and found that he had enlarged, tender lymph nodes on both sides of the neck and ordered hot fomentations. The lymph nodes subsided but the pain and stiffness of the neck persisted so he was referred to hospital. He was pale and was walking about with his head poking forwards, the cervical muscles were tense and there was a depression just below the occiput. Radiographs showed that the second cervical vertebra had slipped forwards on the third and that there was a soft tissue swelling behind the pharynx. He was treated by hyperextension, with a flat pillow under the shoulders, and a head halter with a 1 lb. weight. Next day the radiograph showed some improvement. Ten days later he developed dyspnoea and dysphagia and the radiograph showed that the retropharyngeal abscess had increased in size. Four days later the dyspnoea became urgent and the abscess was palpable in the neck behind the larynx and trachea. It was aspirated by a lateral approach behind the left sternomastoid muscle and 70 ml. of thin pus was obtained. *Streptococcus haemolyticus* was grown. Two days later further aspiration yielded 148 ml. of pus, and this time 100,000 units of penicillin were injected into the cavity. Intramuscular penicillin was also given. A final aspiration three days later yielded 40 ml. and the abscess subsided. Traction in hyperextension was maintained for two months and then he wore a brace for six months. He was last seen, aged 15½ years, and was very well.

S.W., a boy aged 5½ years, jumped off a log nine days earlier and felt pain in the neck. He walked into hospital with his chin cupped in his hand. His mother stated that he kept his chin supported all the time, even when he was eating. His head was poking forwards, the cervical muscles in spasm and he had enlarged tender glands on both sides of the neck. Radiographs showed subluxation of the second cervical vertebra on the third. He was treated by extension with a head halter and 1 lb.

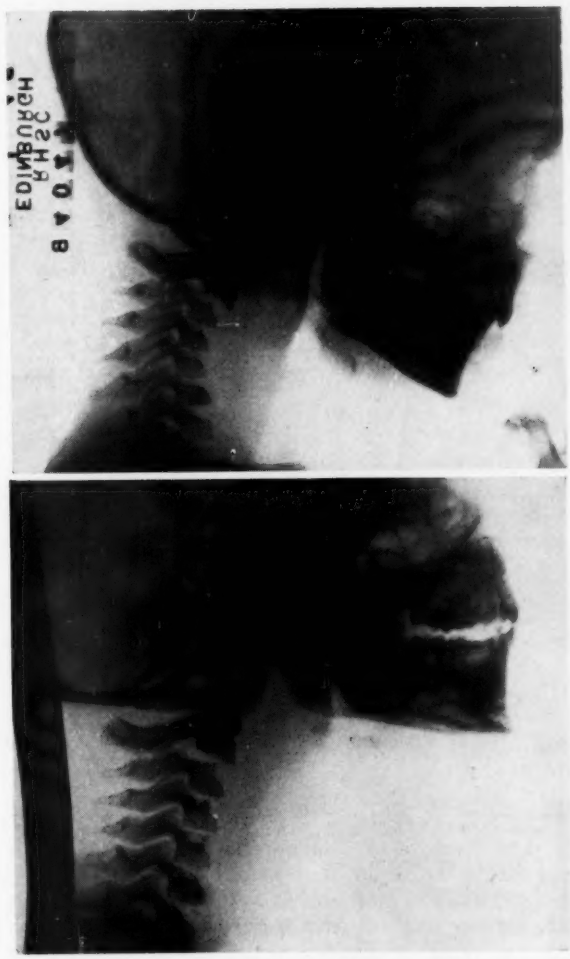

FIG. 1.—Radiograph (above) of Case I.H. on admission, showing retropharyngeal abscess with subluxation.
Radiograph, showing reduction, with the abscess before aspiration.

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

FIG. 2.—Radiograph (above) of Case S.W. showing subluxation of C.2 on C.3 on admission nine days after the injury. Radiograph (below), showing reduction.

weight for 11 days and then he wore a plaster collar for a month.

B.T., a boy aged 8½ years, tripped and fell on his head 10 days before admission. He complained of pain in the left shoulder at the time but not subsequently. Five days later he fell again on the right shoulder but when examined he had full movements of the cervical spine. Five days later he was admitted to hospital with pain in the neck; his head was tilted forwards and to the left. The cervical nodes were not enlarged but he had pharyngitis. Radiographs showed subluxation of the second on the third cervical vertebra. He was treated by head traction for one month, a plaster jacket for two months and a brace for three months.

H.G., a girl aged 1½ years, tumbled backwards on to her head three days before admission. She got up from the floor and appeared to be all right. The next day her mother noticed that she was holding her neck rigidly with the chin jutting forwards. On admission, she had enlarged cervical lymph nodes, and a spasm of the cervical muscles. Radiographs showed subluxation of the second on the third cervical vertebra and also of the third on the fourth. She was treated with head traction for five days, by which time the glands had subsided and the muscle spasm disappeared. She was then allowed to move about in bed as she wished and after 10 days was allowed home. She had no further trouble.

P.H., a boy aged 9, was seized by a severe pain in his neck while dressing. He came up to hospital the same day. His head was tilted forwards and to the left, and the cervical lymph nodes were enlarged. Radiographs showed subluxation of the atlas. The deformity was reduced by head traction.

F.H., a boy aged 3 years, had suffered from coryza for six weeks. The day before admission, while sitting quietly, he suddenly put his hand to the back of his neck and complained of pain. His head was held forwards and downwards. There were enlarged nodes in the left side of the neck. Radiographs showed that the third cervical vertebra was dislocated forwards on the fourth. Reduction was obtained by hyperextending the neck over a pillow and sandbags at the sides of the head. Five days later he was moving about freely in his bed. Supervision was continued for a further five days and, when seen one montn later, he was well with full movement of the neck.

R.H., a girl aged 5½ years, had had tonsillitis and a stiff neck for three weeks. She also had enlarged cervical lymph nodes and radiographs showed dislocation of the second on the third cervical vertebra. She was treated by head traction and afterwards wore a plaster fillet jacket for two months and a brace for a further two months.

M.G., a girl aged 10 years, had attended hospital six months previously with tuberculous cervical lymphadenitis with abscess formation. The abscess had been healed for four months. Two days earlier she had wakened with a stiff neck. She was pale and in pain. She had a severe right-sided torticollis, but no further enlargement of the cervical nodes. Radiographs showed that the second cervical vertebra was dislocated forwards on the third. The dislocation was reduced by head traction and she then wore a plaster fillet jacket for four months followed by a brace for two months. She remained well thereafter.

L.H., a girl aged 10 years, had had her adenoids removed two weeks previously. Two days later she developed a painful stiff neck with a right-sided torticollis. The cervical lymph nodes were enlarged and tender. Radiographs showed that the second cervical vertebra was displaced forwards on the third, and the third on the fourth. She was treated by head traction over a pillow for eight days and then wore a plaster collar for one month.

J.H., a girl aged 6 years, had had her tonsils and adenoids removed 18 days earlier. Four days later she developed a stiff neck. Her head was tilted to the right

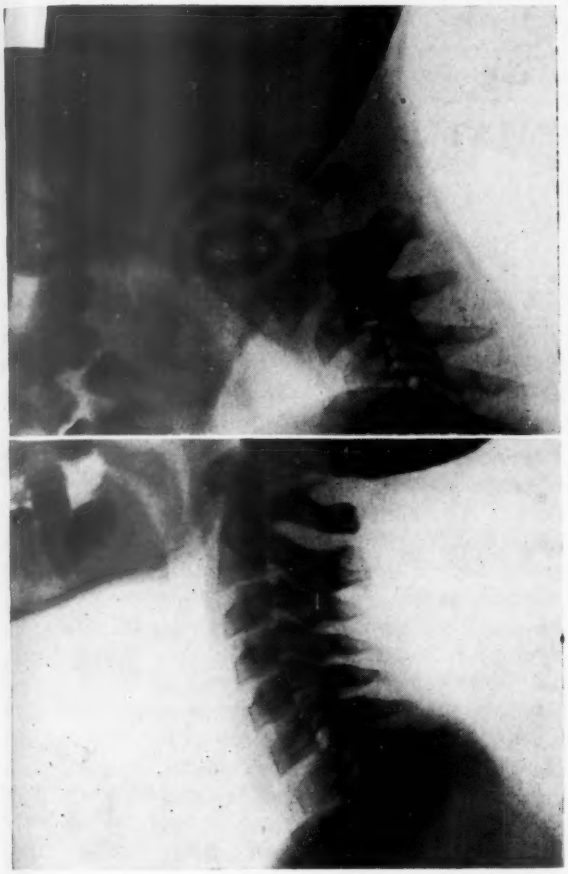

FIG. 3.—M.G. wakened in the morning with a stiff neck. Radiograph (above) shows condition on admission to hospital two days later. Radiograph (below), showing reduction.

and the cervical nodes were enlarged. Radiographs showed dislocation of the second on the third cervical vertebra. The dislocation was reduced by hyperextension over a pillow and eight days later a plaster collar was applied and she wore this for a month.

Discussion

Watson-Jones and Roberts (1934) reported a series of 21 cases of subluxation of the cervical spine in children, but in all their cases the atlas was affected. All the cases were associated with infection, such as tonsillitis, upper respiratory infection, acute mastoiditis or cervical adenitis. One child developed paraplegia but recovered completely.

Sulamaa (1949) reviewed the literature and published two further cases in which the subluxation involved the second cervical vertebra.

In the present series of 10 cases, nine had cervical adenitis and the tenth pharyngitis. The dislocation was multiple in two cases; in only one case was the atlas involved and in the others the second or third cervical vertebra. The spinal cord was not affected and all the children walked into hospital. The length of the history varied from one day to three weeks. No disease was ever demonstrated in the vertebral bodies although all cases were followed up for several months and some even for years, and in no case did the lesion recur. A lateral radiograph taken with the neck in the position in which the child is holding it will usually demonstrate the lesion, but in mild cases the neck has to be flexed or the lesion will be missed.

The cause of the dislocation is hyperaemia of the retropharyngeal tissues, the retropharyngeal lymph nodes and the vertebral ligaments. These ligaments are weakened by the hyperaemia so that minimal trauma or even normal movements are sufficient to produce the dislocation. Thereafter spasm of the cervical muscles prevents further deformity. Reduction can always be obtained by slight hyperextension of the neck obtained by placing a low pillow under the shoulders and it is maintained by light traction with a 1 lb. weight and a head halter, or by placing the head between sandbags with a towel wrapped round them stretched over the forehead. When once the pain, spasm and cervical adenitis had subsided the children were allowed to move about in bed at will in the mild cases. When the infection had been more severe, or the history long, plaster—either as a collar or as a fillet jacket—was used.

Summary

Ten cases of spontaneous dislocation of the cervical spine in childhood are recorded.

All cases were associated with cervical adenitis or infection of the nasopharynx.

The history varied from one day to three weeks and all patients walked into hospital.

No neurological lesions were demonstrated.

All were reduced by simple hyperextension, some with and some without extension.

The results were uniformly satisfactory.

REFERENCES

Sulamaa, M. (1949). *Acta chir. scand.*, **98**, 212.
Watson-Jones, R. and Roberts, R. E. (1934). *Brit. J. Surg.*, **21**, 461.

THE SURGERY OF PREMATURE INFANTS*

BY

P. P. RICKHAM

The spectacular advances in neonatal surgery during the last 20 years have solved many problems which in the past seemed unsurmountable. The advances have, however, raised many problems, amongst which perhaps the most important are those associated with the surgery of premature infants. This paper is presented in the hope of throwing some light upon the many difficulties which beset the surgeon operating upon these tiny infants. It is not suggested that we have solved these problems; we have not. Our operative mortality is very high indeed. We hope, however, that this description of our material and our difficulties will stimulate others to improve the present-day methods so that in the future the surgery of premature infants will be as safe as the surgery of full-term infants is today.

At the present time an operation for a single congenital malformation demanding urgent treatment in a full-term infant is relatively safe. It is true that when studying the reports of large series operated upon in various Anglo-Saxon and European centres we find that the operative mortality for newborn infants is not inconsiderable; this is due to two main reasons, prematurity and multiple malformations. We believe that the operative mortality for infants suffering from multiple severe malformations will remain very high. Moreover, even if these infants survive, they do not usually grow up to become healthy children, but are frequently more or less crippled for life. Prematurity is quite different. If the premature infant survives operation he is likely to develop as well or nearly as well as a full-term child operated upon for the same condition. It is today well known that even grossly premature infants may develop into psychologically and physically normal adults. Hess (1953), who followed up premature infants over several decades, found that 370 infants with birth weights of under 1,250 g. (2 lb. 11 oz.) who were discharged from his unit could be traced. Only 5% of them had died. Of the others, 85% were of average or above average physical development and 90% were of average or above average mental development. There is therefore little doubt that it is worth while to undertake operations in order to save the lives of premature infants.

Incidence

Is the question of prematurity in neonatal surgery of practical importance? How often is it encountered? The literature seems to indicate that operations on premature infants are rare. Surgeons record one or two cases as curiosities and only one extensive series of operations on premature infants has been published. This is the remarkable series reported from the Boston Children's Hospital. In this world centre of paediatric surgery, 159 premature infants were operated upon over a period of 16 years, i.e., an average of about 10 premature infants every year. If these figures represent the true incidence of prematurity in neonatal surgery, then the problem is not worth much consideration.

We were therefore surprised to find an extraordinarily high incidence of prematurity amongst the infants operated upon in our neonatal surgical unit at Alder Hey Children's Hospital (Table 1).

TABLE 1
NUMBER OF NEWBORN INFANTS OPERATED DURING THE LAST FOUR YEARS

	Number of Cases	Deaths	% Mortality
Total ..	405	101	24·7
Premature infants ..	122 (42·3% of all cases)	52	42·3
Full-term infants ..	283	49	17·3

During the last four years we have operated upon 405 infants with 101 deaths, a mortality of 24·7%. One hundred and twenty-two (30%) of these infants were premature. If these are excluded the operative mortality falls to 17·3%. On the other hand, there were 52 deaths amongst the 122 premature infants, an operative mortality of 42·3%, and infants suffering from pyloric stenosis were included in this figure.

The high proportion of premature infants in our cases is easily explained. Practically all infants born

* A paper read at a meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

TABLE 2
OPERATIVE MORTALITY RATE ACCORDING TO WEIGHT COMPARED WITH FIGURES FOR MORTALITY IN PREMATURE INFANTS IN BIRMINGHAM

Weight (g.)	No. of Cases	No. of Deaths	%Mortality	%Mortality (Birmingham)
1,000 and under (2 lb. 3 oz. and under)	2	2	100	95·1
1,001 to 1,500 (2 lb. 4 oz. to 3 lb. 4 oz.)	13	7	53·8	61·5
1,501 to 2,000 (3 lb. 5 oz. to 4 lb. 6 oz.)	38	25	65·7	19·3
Total under 2,000 g.	53	34	64·1	
2,001 to 2,500 (4 lb. 7 oz. to 5 lb. 8 oz.)	69	18	26·1	5·2

with urgent surgical abnormalities in the Liverpool region are transferred to our unit. Supervision of newborn infants by paediatricians, and their diagnosis and transfer is now so well organized that every infant, however small, ill or deformed, finds its way to the centre. If, as it is hoped, more neonatal surgical centres are founded in the various regions of this country, it will soon become apparent that prematurity is a much greater problem amongst surgical cases in newborn babies than was previously supposed.

Classification According to Weight of Infant

According to the classification of the international committee meeting at Geneva in 1937, a premature baby is defined as an infant weighing 2,500g. (5½ lb.) or less at birth and we have used the same criterion. If we divide our small series according to the infant's weight and compare them with 'normal' premature infants who have not been operated upon, we obtain the figures given in Table 2. For comparison we have used the figures given for the City of Birmingham by Crosse (1952). It will be seen that except in the 1,000 to 1,500 g. group, where because of our small numbers we obtain a freak result with an inordinately low mortality, the surgical mortality is considerably higher than that of the normal control. It will be further seen that there is a very definite division of the premature infants surgically treated into two groups. Those above 2,000 g. (4 lb. 7 oz.) have an operative mortality of 26%, *i.e.*, nearly the same as our full-term infants. Of the 53 infants of less than 2,000 g. in weight, 34 died, a mortality of 64%. This statistical survey confirms our clinical experience that the larger premature infants do very well indeed; it is the small ones below 4½ lb. in weight which need so much care and supervision. Below 3 lb. in weight the chances of recovery after operation become very small indeed, which is not surprising when it is remembered that about 80% of normal infants in this weight group will die. All the same we had some spectacular recoveries in this group which show that one should never despair when operating upon newborn infants.

Twenty-two infants in this series had multiple severe malformations and only four of these infants survived operation. Multiple malformations in combination with prematurity appears therefore to be very dangerous indeed.

Classification According to Surgical Conditions

The various conditions can be seen in Table 3. A few points merit discussion. Oesophageal atresia (22 premature infants) holds pride of place. When discussing this condition, the effect of prematurity on surgical results becomes apparent. The overall mortality in the 49 cases of oesophageal atresia which were operated upon during the last four years was 48%, which incidentally is similar to the operative mortality of between 48 and 53% in the half-dozen large series published during the last three years. For full-term infants without associated severe malformations our operative mortality is 23%, but in premature infants it rises to 59%.

TABLE 3
PREMATURE INFANTS CLASSIFIED ACCORDING TO PATHOLOGY

Condition	Numbers	Deaths	% Mortality
Oesophageal atresia	22 (5)	13	59
Pyloric stenosis	20	2	10
Duodenal atresia	12 (3)	5	41·7
Anal atresia	12 (3)	5	42
Malrotation of midgut	9	2	22·2
Exomphalos	9 (5)	7	77·7
Peritonitis	9 (3)	5	55·5
Meconium ileus	7	7	100
Intrathoracic malformations	4 (2)	2	50
Genito-urinary malformations	4	2	50
C.N.S. malformations	4	—	—
Irreducible hernia	3	—	—
Intestinal atresia	3 (1)	2	66·6
Other conditions	4	—	—

Number in brackets=cases with multiple malformations.

The large number of infants with pyloric stenosis is surprising. Only grossly premature infants suffering from this condition are admitted to our unit. Meconium ileus and prematurity seems to be a specially fatal combination; all our seven cases and all Gross's (1953) six cases died. I have been able to find only the record of one premature infant who

survived operation for meconium ileus in the literature (Borenstine and Printz, 1953).

Causes of Death

Necropsy was performed on 51 of the 52 premature infants who died. The main necropsy findings are shown in Table 4. Chest conditions are

TABLE 4
CAUSES OF DEATH

Condition	No
Chest conditions (bronchopneumonia, atelectasis, hypotrophic lungs)	14
Haemorrhagic diathesis	9
Cardiac failure (congenital malformation of heart)	7
Massive venous thrombosis (inferior vena cava, renal veins)	2
Genito-urinary complications (pyelonephritis, absent kidneys)	2
Anastomotic leaks (peritonitis, mediastinitis)	10
Septicaemia (secondary to umbilical sepsis, phlebitis, meningitis)	5
Kernikterus	1
Aspiration pneumonia	1
Total 51 necropsies	

most common (mainly bronchopneumonia and atelectasis, but some cases with absent or hypoplastic lungs). All seven cases of meconium ileus died of bronchopneumonia. There was one death from aspiration pneumonia, which is shown separately, as it is a preventable cause of death. There were 10 anastomotic leaks causing mediastinitis, empyema, or peritonitis according to the site of the anastomosis. This big number reflects on the poor healing quality of the premature infant's tissues especially in the presence of infection. Five further deaths were due to septicaemia, two were secondary to sepsis at the site of intravenous transfusion, one almost certainly secondary to umbilical sepsis, and in the remaining two the cause of the septicaemia was undetermined. Nine children died from haemorrhage, usually widespread. Bleeding into the lungs, retroperitoneal tissues, peritoneum, intracranial cavity, etc., was common, and any combination of bleeding sites was seen. The cause of this bleeding tendency was somewhat obscure. All our infants receive vitamin K pre-operatively; the bleeding and clotting times in all infants were normal. In some there was an absence of platelets; in some no chemical or microscopical abnormality of the blood could be discovered and an immaturity of the capillaries was postulated. Two infants had another intravascular complication, massive venous thrombosis. In one the whole of the inferior vena cava and portal vein thrombosed post-operatively, in the other there was bilateral thrombosis of the renal veins. In seven children death was associated with severe congenital malformations of the heart.

One very premature infant operated for malrotation of the midgut and volvulus died of kernikterus. Kernikterus of prematurity develops when the serum bilirubin level rises above 18 mg. (Meyer, 1956); the cause is often excessive vitamin K administration. At the time of this death we still used vitamin K in dosages of 10 mg. We have since reduced the dosage to 2·5 mg.

The Management of Premature Infants Requiring Surgery

There are several important aspects in the management of premature infants requiring surgery which have to be discussed in some detail.

Anaesthesia. This is not the place to discuss neonatal anaesthesia in detail, but only to point out the differences between premature infants and full-term infants in their reactions to anaesthesia. The liability of the premature infant to pulmonary complications has already been mentioned. It is partly due to the fact that the premature infant's respiratory system is rudimentary both in the histological development of the lung and its mode of ventilation, partly because the cough reflex in premature infants is either deficient or absent. Aspiration of vomitus or mucus is therefore even more common in premature infants undergoing surgery than in full-term babies. In order to minimize the complications, all infants should be nursed in incubators in an atmosphere of 100% humidity, which in our experience is the most important single factor in preventing pulmonary complications. The constant temperature in such incubators allows these infants to be nursed naked so that no clothing or blankets hinder respiratory movements. For the same reason the only type of dressing which we use is a $\frac{1}{2}$ in. broad plastic strip. The infant should be nursed lying on his side, the head slightly elevated, to allow for the maximum freedom of diaphragmatic movement. The position should be changed from side to side every two hours, in order to reduce the chances of massive pulmonary collapse. In cases operated upon for intestinal obstruction constant gastric suction should be prolonged, until all risk of vomiting due to ileus has disappeared. Even in the uncomplicated cases we rarely discontinue suction earlier than the third post-operative day, and often employ it for considerably longer periods. In premature infants operated upon for oesophageal atresia a gastrostomy is always necessary. No feeds are given via the gastrostomy for at least three days after operation in order to minimize regurgitation from the stomach when feeding is started. Feeds are very slowly dripped into the gastrostomy tube and the level of the reservoir is

FIG. 1.—This emergency trolley is standing in the neonatal ward ready for use in any emergency. On the top shelf are laryngoscope, endotracheal tubes, Ree's modification of the Ayr's T piece and rubber bag, various rubber catheters, syringes and drugs. On the bottom shelf stands a powerful electric sucker.

never raised higher than 10 cm. above the infants' abdomen. The baby is not fed orally until it has been shown by 'lipiodol' swallow that there is no hold-up or stricture at the site of the anastomosis.

In spite of these precautions aspiration of mucus or vomitus is all too common. An emergency trolley with endotracheal tubes, laryngoscopes, a powerful electric sucker and rubber catheters thin enough to pass through the endotracheal tubes must therefore always be at hand (Fig. 1) and an anaesthetist skilled in passing these tubes must be constantly on call.

In infants under 3½ lb. in weight pulmonary collapse is very common, because their swallowing and cough reflexes are very rudimentary. Luckily even massive pulmonary collapse can usually be rapidly cured by positioning. Sucking out of the bronchi through an endotracheal tube is only very occasionally necessary and bronchoscopy is only rarely resorted to. This infant, weighing 3 lb. 6 oz., whose radiographs are shown in Figs. 2 and 3 was successfully operated upon for oesophageal atresia but he invariably collapsed the lung on the side on which he lay. He was then nursed for a few hours on the opposite side, which re-expanded the lung lying uppermost, but then the other lung collapsed. This went on for nearly three weeks after operation in spite of the fact that he was entirely fed through the gastrostomy.

The passing of an endotracheal tube does not appear to present any difficulties to the skilled paediatric anaesthetist (even the smallest infant will take an 00 endotracheal tube), neither have there been any complications from this procedure despite the numerous statements to the contrary. There is no great difference in the reaction to anaesthesia between the premature and the full-term infant. Premature infants appear to exhibit the peculiar response of newborn babies to muscle relaxant drugs of the anti-depolarizing type. Frequently they show a myoneural block of the anti-depolarizing type after long administration of drugs of the depolarizing type, such as succinylcholine (Rees and Stead, 1957).

During the first few post-operative days all these premature infants need nursing in an oxygen-enriched atmosphere. Our incubators leak in so many places that the maximum oxygen concentration which is possible is in the neighbourhood of 50%. We have seen no cases of retrolental fibroplasia. This we believe to be due to the fact that it is the concentration of oxygen in the blood that matters. Practically all these premature infants have considerable respiratory difficulties during the post-operative period, and, even in an atmosphere with a high oxygen concentration, oxygenation of blood is imperfect.

Prevention and Treatment of Infections. The most important single factor in the prevention of infection is nursing in a special unit, isolated from all other infants and children. The usual isolation precautions are of course essential. Nursing in incuba-

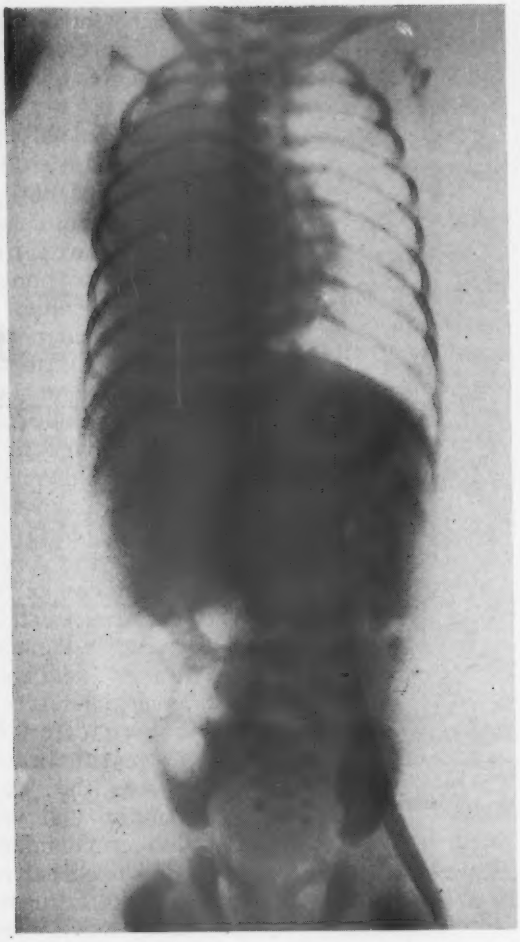

FIG. 2.—Infant of 3 lb. 6 oz. in weight with oesophageal atresia 12 hours after operation. The whole of the right lung is collapsed.

tors further reduces the chances of airborne infections.

All infants receive penicillin and streptomycin before operation and for five days after operation. Although there might be objections to this on the grounds that it may produce the growth of resistant organisms, in practice this method has proved its value. In infants with infective conditions, the organism is cultured, tested for antibiotic sensitivity, and the appropriate antibiotic is given. In cases with fulminating peritonitis when the organism is unknown intravenous terramycin has occasionally been very useful.

Transport. The transport of the larger premature infants, even over long distances (we receive infants from as far away as 100 miles and more) presents no special difficulties. They should be transported in a carry-cot adequately supplied with blankets and hot water bottles. The accompanying nurse must be able to suck out the pharynx and clear the air passages at a moment's notice. The infant should be transported lying flat on his side. A vomiting or distended infant must have a rubber catheter passed into the stomach and the nurse must aspirate the stomach at 10-minute intervals.

Infants under 4 lb. in weight are best transported in a portable incubator at a temperature of 85° F., an atmosphere of 100% humidity and an oxygen concentration of 50%. We have a home-made incubator, which we send out when the condition demands it (Fig. 4).

Control of the Body Temperature: Sclerema. It has been known for a long time that because of their relatively large body surface and immature temperature regulating centres premature infants need to be

FIG. 3.—The same infant as in Fig. 2 three hours after the first radiograph was taken. The right lung has re-expanded. There is now collapse of the left lung. In the period intervening between the two radiographs the infant was lying on his left side.

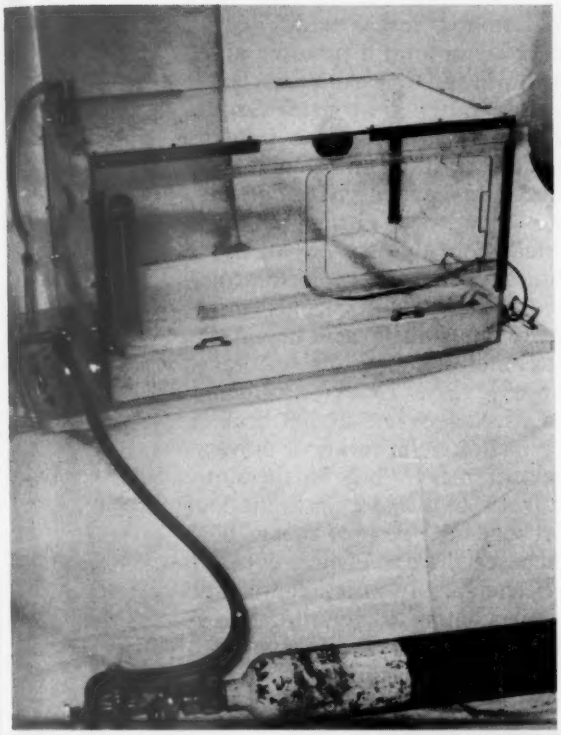

FIG. 4.

FIG. 4.—This portable incubator is heated by a hot water tank beneath the mattress. Infants are transported in a high oxygen concentration and an atmosphere of 100% humidity. There is a large sliding door and an attachment facilitating gastric suction.

kept at a high environmental temperature. Full-term infants can be operated upon without any special protection against heat loss; the body temperature often drops to 90° F. or below without any ill effects. Premature infants, however, stand a fall of body temperature very badly; they should therefore be nursed in incubators at a temperature of 90° to 95° F. The special surgical incubators we use are so designed that the infant can be continuously nursed inside them (Fig. 5). Large side flaps allow handling and feeding of the baby without an appreciable lowering of the temperature. The infant lies on a plastic tray, which can be tilted from the outside and which is radio-translucent, so that radiographs can be taken while the child is in the incubator. The incubator has its own oxygen supply and an attached drip stand, which allows the infant to be transported in the incubator from the ward to the operation table.

At operation these infants are placed on an electric, thermostatically controlled blanket and wrapped as far as possible in gamgee wool. They are returned to the incubator immediately after operation.

There is one post-operative complication, which

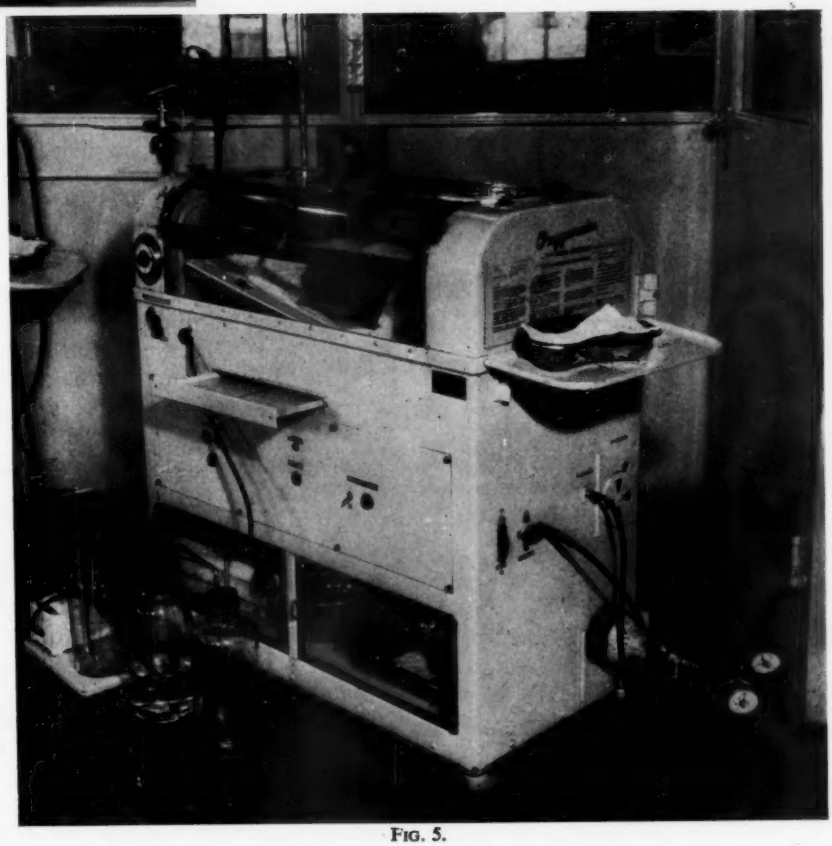

FIG. 5.

FIG. 5.—Premature infant nursed in a surgical incubator. The incubator has a double hinged lid, allowing for the small side doors to be opened without a marked fall in the temperature, humidity and oxygen concentration. Transfusion stands are incorporated in the design. The baby is nursed on a radio-translucent tray. The drawer underneath facilitates the introduction of *x*-ray plates.

we have as yet not discussed, although it causes perhaps more deaths of operated premature infants than all the conditions mentioned above; this is sclerema neonatorum. This condition, which is supposed to be a very rare one, is characterized by a hardening of the subcutaneous fat, due, it is presumed, to solidification. Although sclerema was recognized in the eighteenth century (Usenbenz, 1722; Underwood, 1784) the condition is still very incompletely understood. It occurs in infants who are exposed to cold, but is so rare that even single cases are reported in the literature. We have found that in very ill premature infants who undergo severe operations, especially if operation is coupled with post-operative infection, some degree of sclerema is invariable. If sclerema were due to exposure of the infant to low temperatures, one would suppose that it would be noticed immediately after operation, as this is the only time the infant is outside the incubator. This is not so; the condition usually develops during the second, third, or fourth post-operative day. If severe, the infant will succumb within 24 to 48 hours of pneumonia secondary to respiratory difficulties. Nearly half of our premature infants who died had some degree of sclerema, but this is not recognized at necropsy, because of the stiffness of rigor mortis. Sclerema, therefore, does not figure as a cause of death at necropsy.

We have found that the treatment of sclerema is very difficult. The accepted method of treatment consists in the administration of cortisone in doses of 10 to 25 mg. t.d.s. (Wickes, 1956). We have used this method for over three years, but we found that in premature infants who have undergone an operation it is most unsatisfactory. In these infants cortisone inhibits healing and anastomotic leaks readily occur. After laparotomy a ruptured abdomen, which in our experience is the greatest rarity in neonatal surgery, is not at all uncommon (Fig. 6). Because of these unfortunate side-effects, we stopped giving cortisone and have tried giving D.O.C.A. instead on the somewhat hypothetical basis that mineralocorticoids and glucocorticoids might have antagonistic actions on the intercellular ground substance (Foster, 1957). However, although D.O.C.A. does not inhibit healing, it is ineffective in curing or preventing sclerema. We have, therefore, returned to the administration of cortisone in doses of 5 mg. b.d., whenever there is clinical evidence of sclerema. In addition we raise the incubator temperature to between 98 and 100° F. and attempt to administer a maximum of glucose either orally or intravenously. The cortisone is immediately discontinued when the sclerema begins to subside. This treatment has on the whole been quite successful and gross sclerema has only rarely developed since this regime has been employed.

FIG. 6.—Infant weighing 3 lb. 8 oz. at birth who was operated on for intestinal atresia. Post-operatively she was put on cortisone and the abdomen ruptured and was resutured. At 7 months of age she has a large incisional hernia.

Fluid and Electrolyte, Plasma, and Blood Therapy. This is not the place to go into detailed consideration of fluid and electrolyte therapy (Rickham, 1957). Kidney function in premature infants is poor. If there is no gross dehydration and no post-operative fluid loss, as for instance, in oesophageal atresia, the premature infant does not usually require any fluids for two to three days after operation. After abdominal operations necessitating continuous post-operative gastric suction, 5 ml. of fluid per hour is the maximum intravenous requirement. In order to administer accurately such small quantities, it is important to incorporate a burette measuring up to 1 ml. in the intravenous set (Fig. 7). It is extremely easy to over-infuse a premature

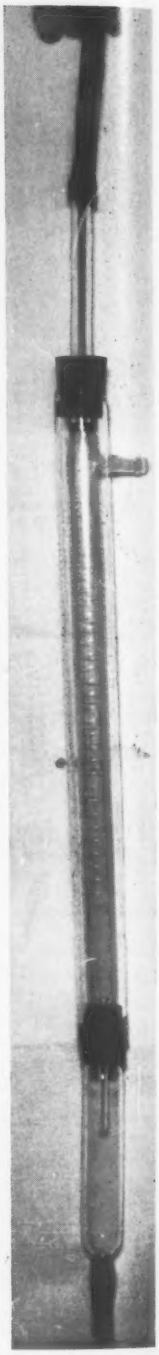

FIG. 7.—Measuring burette holding 30 ml. and graduated in millilitres incorporated into an intravenous giving set.

infant and so to produce fatal pulmonary complications.

The sodium and chloride requirements of the premature infant are also small. If there has not been any vomiting nothing but 5% glucose water should be infused for dehydration. With continuous gastric suction N/5 normal saline and 5% glucose is the infusion of choice.

Premature infants need hardly any potassium replacement as there is no post-operative potassium shift. When continuous suction is employed for more than three days, some potassium should be replaced. This is conveniently done by giving small (30 to 40 ml.) daily infusions of Darrow's solution.

The serum protein level of premature infants is always low and falls rapidly during starvation. While the infant is on intravenous therapy it is best to replace proteins by infusing small daily amounts of half-strength plasma. This is important, as a low plasma protein concentration may easily produce generalized oedema, or aggravate the oedema often present in newborn premature infants.

The haemoglobin concentration of premature infants at birth is usually very high. Nevertheless any blood loss at operation should be meticulously replaced and even slight over-transfusion at operation does not do any harm. During the first few weeks of life the haemoglobin level drops sharply and anaemia is common (Arthurton, O'Brien and Mann, 1954). Iron preparations must be administered and occasional small blood transfusions are very valuable.

The sooner the infant can come off intravenous therapy and alimentary fluids can be taken the better. Starting with 1 dram of glucose water, given every two hours, the amount is gradually increased. When the amount has reached 4 drams two hourly, half strength breast milk should be given. When the feed reaches 6 drams two hourly, full-strength breast milk is substituted. The bigger infants take feeds readily from a pipette, the smaller may occasionally need feeding by gavage. In cases operated upon for intestinal obstruction a tube should be passed into the stomach before each feed and the stomach aspirated for the first 48 hours after feeding has started. If more than 10 ml. are aspirated the oral feeds must be decreased or stopped. After 48 hours the tube needs only to be passed four hourly, after 72 hours, six hourly, and suction can usually be discontinued after the fourth day. This method might seem unduly elaborate, but it ensures that there is little chance of vomiting and obviates the danger of aspiration. In general we do not start feeding by bottle before the child weighs 4½ lb. and bottle feeding is then only gradually introduced.

Once the infant is on full feeds it must be remembered that the premature infant needs 3 oz. of milk per pound of body weight, and that the infant who has undergone a severe operation and subsequent weight loss may need even more. We have occasionally given 3½ or 4 oz. of milk per pound of body weight before the child started to gain weight.

Surgical Technique. This does not differ in any respect from that employed in operating upon full-term infants. It goes without saying that without a really good operating light, small instruments and the finest needles and sutures it is futile to attempt operations. In very small infants anastomosis may be a strain on the eyes and there may be a place for

FIG. 8.—The smallest infant to survive operation, a premature infant weighing 2 lb. 8 oz. operated upon for pyloric stenosis.

FIG. 9.—Same infant as in Fig. 8 when 13 months old.

FIG. 10.—Smallest infant with oesophageal atresia to survive (birth weight 2 lb. 15 oz.).

FIG. 11.—Same child as in Fig. 10 when 20 months old.

FIG. 12.—The smallest child with intestinal atresia to survive operation (birth weight 3 lb. 4 oz.).

FIG. 13.—Same child as in Fig. 12 when 9 months old.

operating magnifying spectacles such as are used by many American paediatric surgeons.

Discharge and Follow-up. The infants are discharged when their condition is satisfactory and when they weigh at least 5 lb. It is advisable to admit the mother two or three days before the infant's discharge in order to accustom her to looking after the baby. The infant should be established on one of the dried milk preparations before discharge. After discharge the supervision of these infants has been made much easier by making use of the premature infant district nursing service which has been established in Liverpool. The infants are followed up in the Out-patient Department. On the whole their subsequent progress has been most satisfactory (Figs. 8, 9, 10, 11, 12, 13).

It is perhaps one of the most gratifying experiences in surgical practice to watch such a premature infant developing through the months and years. Most of them do very well indeed. The surgery of premature infants is full of disappointments and an inordinate amount of labour has to be expended in order to achieve occasional successes but the few successes make it all very much worth while.

This paper is based on the work of a large team. Space does not allow me to mention all those who have helped. About half the cases included in this paper were operated upon by Miss Isabella Forshall. I wish to thank her for her help and advice and for assistance in the preparation of this paper. Dr. G. J. Rees and Dr. A. Stead, consultant paediatric anaesthetists to the Unit, have given invaluable assistance, not only by their skill in the administration of the anaesthetics, but also by their help in pre- and post-operative supervision. Dr. E. G. Hall and Dr. C. Jones, pathologists to Alder Hey Children's Hospital, have supplied much of the information upon which this paper is based. Mr. J. T. Ireland has been responsible for the biochemical data for control of treatment.

I should like to make special acknowledgment of the devoted and skilful work of our sisters and nurses, especially Miss J. M. Jenkins, Sister-in-Charge of the Neonatal Surgical Unit.

REFERENCES

Arthurton, M., O'Brien, D. and Mann, T. (1954). *Arch. Dis. Child.*, **29**, 38.
Borenstine, J. and Printz, J. H. (1953). *J. Pediat.*, **43**, 208.
Crosse, V. M. (1952). *The Premature Baby*, 3rd ed. London.
Foster (1957). Personal communication.
Gross, R. E. (1953). *The Surgery of Infancy and Childhood.* Philadelphia.
Hess, J. H. (1953). *Pediatrics*, **11**, 425.
Meyer, T. C. (1956). *Arch. Dis. Childh.*, **31**, 75.
Rees, J. G. and Stead, A. L. (1957). Personal communication.
Rickham, P. P. (1957). *The Metabolic Response to Neonatal Surgery.* Cambridge, Mass.
Underwood, M. (1784). *A Treatise on the Diseases of Children.* London.
Usenbenz, J. A. (1722). *Academiae Caesareae-Leopoldino Carolinæ. Naturae curiosorum Ephemerides*, Centuria IX, p. 57.
Wickes I. G. (1956). *Arch. Dis Child* **31**, 419

THE PATHOLOGY OF CONGENITAL RING CONSTRICTIONS*

BY

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There is no agreement about the cause of the constrictions at birth on various parts of the human body. This paper suggests that they are due to the digits, limbs or the body itself penetrating to various degrees the amniotic membrane, with consequent concentric pressure on the developing tissues. The conditions necessary for a final testing of this hypothesis are laid down.

Characteristics of Ring Constrictions

1. They increase in frequency with their nearness to the extremities of the body, being very common in the fingers and toes, less common on the limbs and extremely rare on the body. I have seen one case with a typical one right round the lower thorax, but have not heard of another.

2. It is common to find two or more digits fused together at their tips, with a ring constriction round the fused region, while their proximal parts are separate.

3. The constrictions may vary from a slight groove in apparently normal skin and subcutaneous tissue to such a depth that the part distal to them may fall off, either before or after birth. In the deeper ones ulceration of the bottom of the groove at birth is usual. Intermediate depths may cause atrophy and paralysis of the distal parts, with or without lymphatic oedema. This oedema subsides after excision of the ring and joining of the skin on either side of it.

4. Occasionally there are constrictions at two levels on a limb, for instance, round the tips of the toes and also round the ankle.

5. There may be an acute bend of the bones at the site of the constriction. I have seen this only in the leg.

6. Club-foot and other deformities of the feet are frequently associated with constrictions.

7. In certain cases strips of tissue resembling necrosed amniotic membrane are found in the constrictions. This only occurs when they are very deep, with ulcerated bases.

8. It has been noted in many cases that the amnion is irregular and torn or shredded, apart from showing 'amniotic bands' in some cases, but not in all.

9. Apart from the occasional talipes moulding of the feet which has been mentioned, the children are normal, with no sign of excessive mechanical or hydraulic intra-uterine pressure.

10. An important case in my argument, though there were no constrictions on the child, is a surviving girl from an extra-membranous pregnancy. She is now a normally active child though she had a club-foot and suffers from Turner's syndrome.

I suggest that this whole picture can be explained by the assumption that these children have got their digits, their limbs, half their body, or in the case of extra-membranous pregnancies, their whole body, through or into holes in the amnion. To illustrate the mechanism one can cut a round hole in a piece of rubber sheeting and thrust a wax candle through this hole so that the rubber is firmly contracted on the wax. If the wax is then softened by heating in hot water the contracting rubber will mark it in a ring constriction very like those found on the body. Obvious modifications of the experiment will reproduce the typical fusions of digits at the site of the constriction.

The shreds of necrotic amnion found in some ulcerated constrictions can be reasonably explained as the products of a mutual compression between the constricting ring of the perforation and the limb gripped by it; pressure high enough to cause the sloughing of the foetal skin must also be high enough to kill the amnion in immediate contact with it. As the gripped limb is torn out it brings the necrotic ring with it.

Constriction rings at different levels on a limb could be the results of a limb which had originally penetrated only a short way into the amnion subsequently being thrust deeper.

The importance of the case of extra-membranous

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

FIG. 1.—Newborn baby with congenital constriction of the left leg. Note oedema below the constriction.

FIG. 3.—Case shown in Fig. 1 after (*a*) excision of the constriction; (*b*) osteotomy on right-angle bend of the tibia and fibula at the site of constriction; (*c*) correction of club-foot moulding of both feet. The child is now, at the age of 7, very strong and active on her feet.

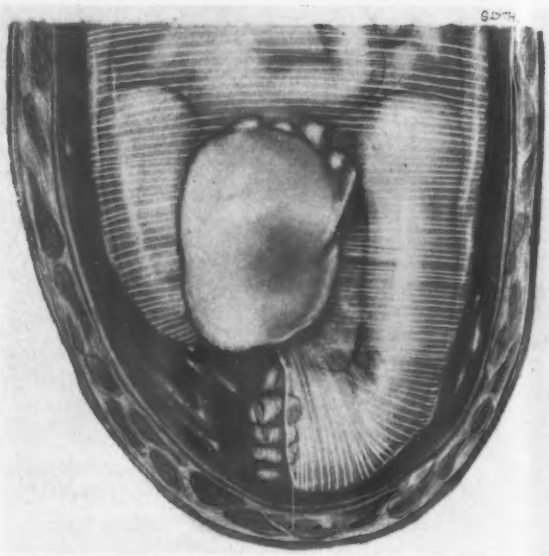

FIG. 2.—Hypothetical diagram of the intra-uterine conditions that may have been responsible for the constriction shown in Fig. 1. The amnion is represented as a transparent sheet by fine parallel lines.

pregnancy (Lawlor, 1949) is that if a child can escape wholly from the amniotic case it is reasonable to assume that partial escapes may also occur, and that they would be much more frequent; the frequency diminishing as the degree of the escape increases.

Streeter (1930) has suggested that the rings are due to intra-uterine ulceration in a ring form, resembling a tropical disease called ainhum. Objections to this are: (1) Many of the slighter constrictions show no evidence of ulceration ever having been present. (2) This ulceration could not cause the fusing of the tips of the digits since the raw areas, which alone could fuse, are at the bottom of the grooves and cannot meet each other. (3) It cannot explain a ring round the body; one cannot imagine an annular degeneration of this kind there. (4) It gives no explanation of the shreds of necrotic tissue in the deep clefts; processes of ulceration never produce anything like these.

Many authors have suggested amniotic bands as the cause (Lennon, 1947; Grob, 1957). A few experiments with a limb of modelling clay and a 'band' of any kind, say a piece of tape, will show that it is quite impossible to produce any ring marking in this way.

It is important to note that in my opinion the condition, seen most frequently in the forearm, in which the limb ends suddenly, usually with rudimentary digits, is a totally different one, due to simple failure of development.

Various points remain to be investigated along the lines I have suggested. The first essential is the

FIG. 4.—Similar case to that in Fig. 1.

FIG. 5.—Typical congenital constrictions of the fingers, showing fusions and amputations.

FIG. 6.—Typical constriction rings, fusions and amputations of toes.

FIG. 7.—Constriction ring of the left leg so severe that the distal part became gangrenous and dropped off soon after birth. Note club-foot deformity of the other side.

preservation and careful study of the whole of the membrane in a case of the sort. Unfortunately the placenta is seldom studied, and the membranes almost never. It would be necessary for proper examination to have some sort of a mould about the size of the folded foetus, upon which they could be pinned and fixed for investigation. Then there is the stage of pregnancy at which the penetration of the amnion occurs to be determined. The common fusing of the digits suggests that this is very early, before they have separated.

REFERENCES

Browne, D. (1936). *Proc. roy. Soc. Med.*, **29**, 1409.
Grob, M. (1957). *Lehrbuch der Kinderchirurgie*. Stuttgart.
Lawlor, M. K. (1949). *J. roy. Soc. Med.*, **42**, 64.
Lennon, G. G. (1947). *J. Obstet. Gynaec. Brit Emp.*, **54**, 830.
Streeter, G. L. (1930). *Contr. Embryol. Carneg. Instn*, **22**, 41.

A TREATMENT OF UNDESCENDED TESTICLE IN INFANCY*

BY

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This study is based upon the examination of 2,700 newborn boys. The original purpose was to find out how often the testicle was undescended at birth and what happened in such cases during the first few months of life.

It is not difficult to feel the testicle of a newborn boy if it be lying outside the external inguinal ring. Examination may only become uncertain, and at times impossible, when the natural increase of subcutaneous fat and the activity of the cremaster muscle combine to conceal the organ in the groin. These events, however, do not occur until the age of 6 months or more and even then are usually insufficient to cast doubt on the findings.

Because the testicle can be felt in the scrotum at birth it is possible to measure its distance from the pubic crest with reasonable accuracy. By so measuring, a standard can be established by which to judge whether descent has, or has not, taken place. The suggested figure in this investigation is 4 cm. ($1\frac{1}{2}$ in.): at this point the testicle can lie comfortably in the scrotum.

This standard represents a minimum distance in a full-term infant (5 lb. 8 oz. or more) and it continues to be valuable for many years. It is normally found that in both infants and boys up to puberty the testicle lies between 4 cm. and 8 cm. from the pubic crest, depending largely on the degree of scrotal contraction. In adolescence, owing to increase in size of both testicle and scrotum, the normal distance is greater.

Cases Investigated

In this series 2,700 boys have been examined in the maternity department of a general hospital. Where one or both testicles was found to be incompletely descended a follow-up was continued for at least one year and in most cases much longer.

One hundred and eight boys were found to have the deformity (see table). Of these, the testicle was observed to descend in 89 during the first 12 months of life, almost exactly two-thirds (60) during the first month. Of the remaining 19, in five the testicles did not appear to have changed position (they were small and at the external ring), three had never been felt and were presumably within the inguinal canal or abdomen, and 11 persisted just outside the top of the scrotum.

The Obstructed Testicle

It is with this latter group of 11 that curiosity was aroused. Why was there no advance into the scrotum? There were three distinctive features about these cases. First, the testicle was present at birth or appeared within the first few days of life. Second, it was of good size and firm consistency, and third, it did not alter in position during many subsequent weeks or months of observation; it remained at the pubic crest or, at most, could be pushed 1 to 2 cm. below it. Any attempt to push or pull it into the scrotum was unavailing.

FOLLOW-UP OF 108 CASES

Descended in one month	60
Descended between 2nd and 12th months	29
No advance since birth	5
Descent apparently obstructed	11
Never felt	3
Total	108

On three or four occasions these infants produced a herniation into the unclosed processus vaginalis during the first three months. In treating the hernias by surgical excision of the sac, I was interested to find that the pathway from the external ring to the scrotum was blocked by a definite septum, or fibrous barrier, which had to be broken through by firm pressure before the scrotal cavity could be reached (Fig. 1). This septum lies at the junction of the smooth inguinal and corrugated scrotal skin. It forms the bottom of the 'superficial inguinal pouch'. Browne (1938) described it as 'an abnormal attachment of the fascia of Scarpa to the pubic bone'. He went on to say, 'This means that instead of the in-

* A paper read at the meeting of the British Association of Paediatric Surgeons in Edinburgh in June, 1957.

guinal pouch having an open lower end, the way from it into the scrotum is blocked by a strong fibrous hammock in which the testis lies supported.'

If these observations be correct it is clear that the cause of failure of descent is an obstruction and is not inherent in a deformity of the testicle or a shortness of the cord. The rational treatment is therefore to remove the obstruction at an early age to enable the testicle to descend spontaneously or to place the organ in its normal position. The policy of waiting and the subsequent use of hormones is unlikely ever to be rewarded.

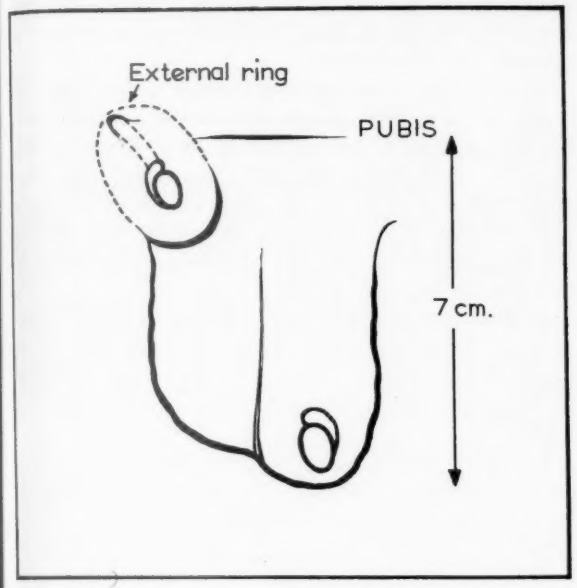

FIG. 1.—Diagram to represent the superficial inguinal pouch closed at its lower end.

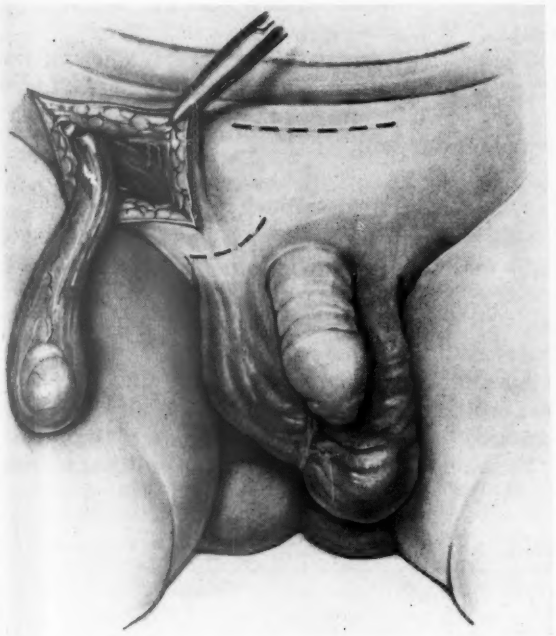

FIG. 2.—Testicle and cord dissected free. Interrupted lines represent levels of pubic crest and septum. Note smaller size of scrotum on the affected side.

A Surgical Treatment

Operation was undertaken in 11 cases and the results have been reasonably satisfactory.

The technique is simple. By an incision over the external ring the superficial inguinal pouch is entered. The testicle and cord with their coverings are dissected clear (Fig. 2). The tunica vaginalis is opened and explored with a probe to find out if it communicates with the peritoneal cavity. If a hernia be present the sac is dissected off the cord and ligated as high as possible.

The lower end of the superficial inguinal pouch is then broken through with firm pressure by the little finger (Fig. 3). A stitch of nylon is passed through the gubernaculam, which at this age is a thick and strong structure attached to the lower pole of the testicle. Both ends of the nylon are threaded into the inguinal incision and out through the bottom of the scrotum, thus drawing the testicle down towards its normal position. After closing the inguinal wound the stitch is attached to the skin half-way

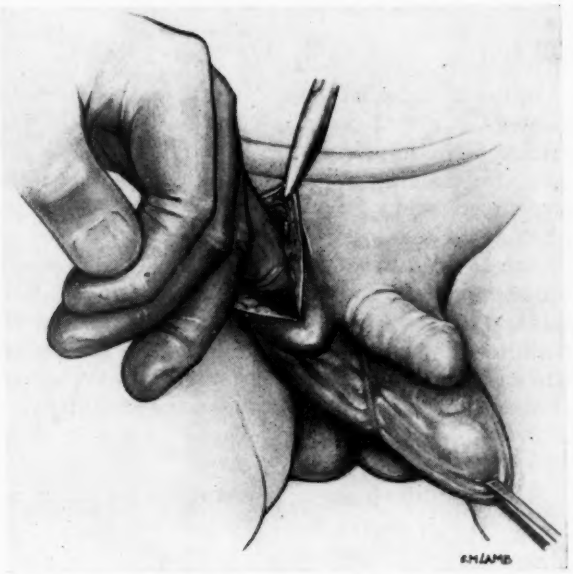

FIG. 3.—Septum about to be broken through with the little finger.

down the inner side of the thigh (Fig. 4). In one case where this stitch was not used, the testis, encouraged by the application of napkins, slipped back into the groin after operation, and became fixed in that position. The stitch is kept in for two or possibly three days and tight napkins are not allowed for several days.

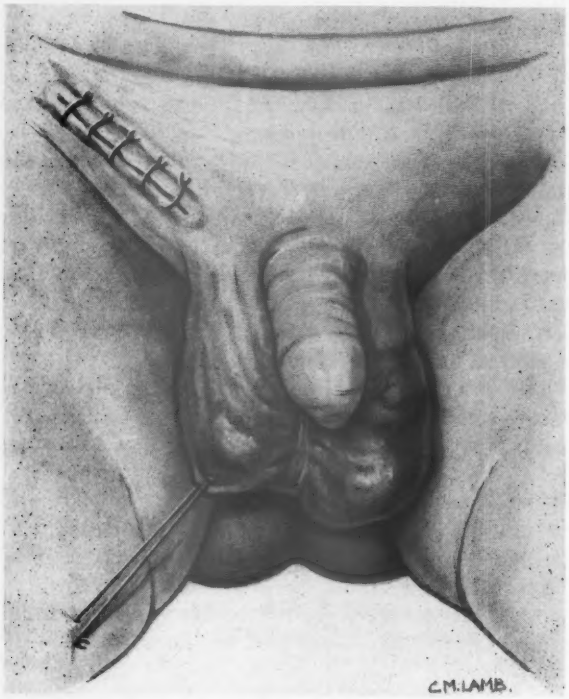

FIG. 4.—Nylon stitch holding the testicle in the scrotum.

Results

In the 11 infants treated 10 now have the testicle between 5 and 7 cm. from the pubic crest. The testicle cannot always descend fully because the scrotum is often smaller on the side where the obstructing septum is found. In one of the cases obstruction was bilateral.

Age at operation varied between 3 and 52 weeks but the majority of infants were under 3 months, and this appears to be the most satisfactory time from the point of view of results. The testicle is of average size and firm. The cremaster muscle is not removed at operation so retractile activity occurs normally.

Discussion

This operation is not new in concept but, as far as I know, has not been advised before as a definitive treatment in infants. It may well be criticized for three reasons.

Is it right to do inessential surgery in an infant? With modern anaesthesia and care the risk of surgery is evidently no greater than in the adult. Hospital admission is only necessary for two to three days and feeding is interfered with to the extent of missing only one meal.

Is it not probable that the testicle would descend if left alone? This group of cases of undescended testicle appears to correspond to what Browne calls 'superficial inguinal ectopia', for which he says operation is essential. In addition there is some evidence that if the testicle does not descend during the first few months of life it is unlikely ever to do so (Scorer, 1955).

Is there not a danger of injuring delicate structures? All surgical procedures can be dangerous or cause damage unless properly carried out. In some respects an infant's tissues are easier to handle than a boy's.

In favour of the operation is correction of a congenital deformity early in life. It is not yet known at what age spermatogenesis becomes permanently limited in the retained testicle but it may at least be impaired if the testicle is allowed to remain in the groin during boyhood. Moreover, in infants with undescended testicles a hernia is much better treated surgically than with a truss; six of the 11 cases had hernias and in two of the others a sac was not sought.

There seems to be, therefore, some rational grounds for considering the possibility of treating by surgery those infants in whom a failure of testicular descent is due to obstruction.

Summary

In the examination of 2,700 newborn infants, 18 cases were found in which one or both testicles did not descend into the scrotum during the first year of life. Of these, 11 appeared to have an obstruction to descent.

A simple operation is described to break through the obstruction and bring the testicle into the scrotum.

The value of the operation is critically discussed.

REFERENCES

Browne, D. (1938). *Brit. med. J.*, 2, 168.
Scorer, C. G. (1955). *Brit. J. Urol.*, 27, 374.

BACTEROIDES INFECTION IN THE SURGERY OF CHILDHOOD*

BY

A. A. GUNN

From Western General Hospital, Edinburgh

Death from acute appendicitis in childhood is now so rare that its occurrence calls for a retrospective study of any unusual features of the case. A fatal case with complications apparently associated with or the result of infection by the bacteroides group of organisms prompted an investigation into the part played by these bacteria. A review of the literature and one fatal and one surviving case were the subject of a previous paper (Gunn, 1956). Since that time five further cases of bacteroides infection have been encountered. It is the purpose of this paper to record these cases and to emphasize the importance of the early recognition and treatment of this infection. An account is given of the problem as it presented to us.

Case 1. A girl aged 8 years was admitted with a 48-hour history of abdominal pain beginning centrally, spreading to the right iliac fossa and accompanied by nausea and vomiting. The clinical findings were: temperature 101·8° F., pulse rate 120 per minute, tenderness localized to McBurney's point with guarding in the right iliac fossa and rebound tenderness in both iliac fossae, bowel sounds present but faint, white cell count 8,000 per c.mm. A diagnosis of acute appendicitis was made and, at operation two hours later, a gangrenous, unperforated appendix was removed from the pelvis. There was no obvious spread of infection beyond the appendix and the wound was closed without drainage. The appendix contained Gram-negative bacilli and Gram-positive cocci. There was no growth on aerobic culture and anaerobic cultures were not made.

Penicillin and streptomycin were given intramuscularly for the first 48 hours but the general condition did not improve and terramycin was then substituted.

Late on the second post-operative day the child's condition deteriorated rapidly over a few hours. Repeated abdominal examination revealed bruising spreading rapidly around the gridiron incision. The diagnosis of intraperitoneal haemorrhage after slipping of the ligature on the appendicular artery was made and after resuscitation with blood and plasma laparotomy was carried out. When the gridiron incision was opened, the rectus and oblique muscles were black and necrotic with evil-smelling grey pus between the muscle layers. There was no evidence of peritoneal haemorrhage or leakage from the appendix stump. A specimen of pus was taken for investigation and the wound edges were apposed with a few interrupted sutures.

The subsequent course was marked by the development of infective lesions in the superficial tissue, the pleural and pericardial cavities and the subphrenic areas (Figs. 1 and 2). Treatment consisted of aspiration and drainage as indicated, blood transfusion (5 pints over 15 days) to counter a falling haemoglobin level and an attempt at antibiotic cover by repeated sensitivity tests, the reports of which were only received after a necessary delay of four days. The organisms isolated, their sensitivity to antibiotics, and the antibiotics administered are detailed in Fig. 3. Penicillin and streptomycin were discontinued because of lack of response and terramycin was substituted. Erythromycin was added because of the passage of loose stools which were sug-

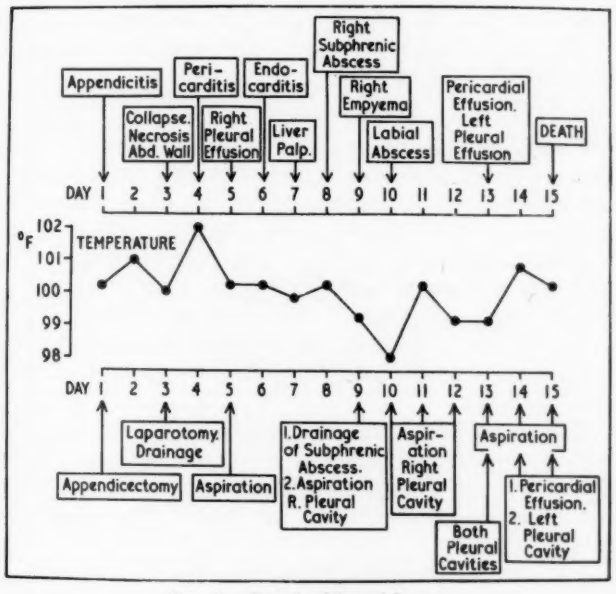
Appendicitis
Peri-carditis
Endo-carditis
Right Subphrenic Abscess
Right Empyema
Pericardial Effusion. Left Pleural Effusion
Collapse. Necrosis Abd. Wall
Right Pleural Effusion
Liver Palp.
Labial Abscess
DEATH
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
°F 102 101 100 99 98
TEMPERATURE
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Laparotomy. Drainage
Appendicectomy
Aspiration
1. Drainage of Subphrenic Abscess. 2. Aspiration R. Pleural Cavity
Aspir-ation Right Pleural Cavity
Aspiration
Both Pleural Cavities
1. Pericardial Effusion. 2. Left Pleural Cavity

FIG. 1.—Case 1, girl aged 8 years.

* A paper read at the meeting of the British Association of Paediatric Surgeons held in Edinburgh in June, 1957.

FIG. 2.—Chest radiograph showing pericardial and right pleural effusions.

gestive of staphylococcal enteritis. A further report showed that all the organisms were sensitive to chloramphenicol which was given but the next report suggested that the sensitivity had changed and that penicillin was the drug of choice. This was probably the crucial point as a later report showed that the bacteroides were no longer sensitive to penicillin and from the tenth to fourteenth days the patient received an antibiotic to which the organism was resistant. Death occurred on the fifteenth day.

The Organism

The bacteroides are a group of Gram-negative, non-sporing, non-motile anaerobic bacilli. They are haemolytic and necrotizing and some are gas-producing. An important characteristic is that these organisms are slow to grow on culture media and may not appear for well over 48 hours. In consequence infection of this variety is often missed, since it is common laboratory practice to discard anaerobic cultures that are negative after 48 hours.

The organisms are of several types and bacteriologists are undecided on their classification. Alston (1955) records the various synonyms and terms infection due to them 'Necrobacillosis'.

For clinical purposes two main groups can be identified.

(1) *B. funduliformis*, pleomorphic, cocco-bacillary in early infections and later becoming filamentous; these are the more pathogenic variety and are associated with a high morbidity and mortality. (2) *B. fragilis* are small bacilli of constant form which produce local infections but only rarely septicaemia.

The organisms are normal commensals of the mucous membrane of the mouth, the intestinal and urinary tract and the female genital organs. Under unusual circumstances—generally in a mixed infection with anaerobic streptococci—they may become pathogenic.

Two factors seemed to play a part in the development of pathogenicity: a surgical operation and, as King, Conklin and Collette (1952) suggested, an inherently inferior defence against this type of infection. Thus, when the associated organisms were overcome the bacteroides were still able to proliferate. It is possible, therefore, that bacteroides infection may occur more frequently now that the more usual pathogenic organisms can be effectively controlled by antibiotics.

The recognition of the part played by the bacteroides group of organisms in Case 1 prompted a review of the literature which was the subject of a previous paper and only a brief summary is given here. Records of 330 cases were found and in 148 there was bacteroides septicaemia. There was no difference in the sex incidence, the maximum incidence being from 10 to 40 years although males are

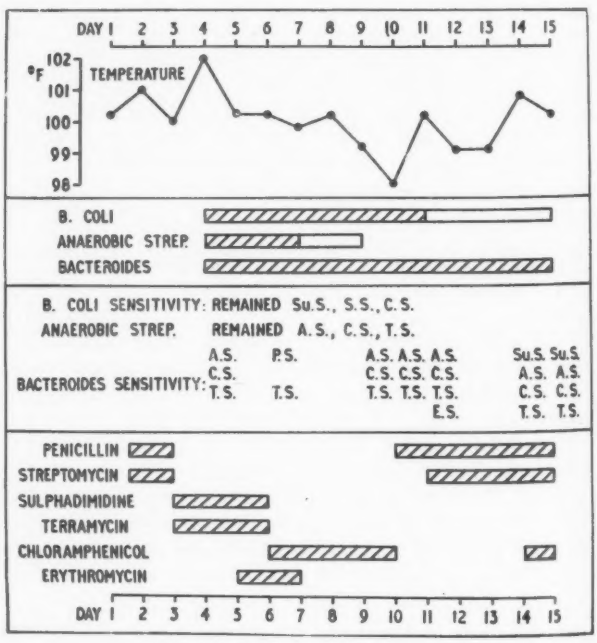

FIG. 3.—Case 1, girl aged 8 years.

affected at all ages most of the female cases occur between 20 and 30 years.

Bacteroides septicaemia is always serious. Before the introduction of sulphonamides the mortality rate was 80%, with sulphonamides over 50% and after antibiotics became available the mortality rate remained 33%.

The primary lesions in the septicaemic cases occurred in the nasopharynx, alimentary tract, middle ear, female genital tract and in traumatic wounds. Further reference is made only to the primary lesions which are of importance in childhood.

Nasopharyngeal Infection. This is the most frequently reported source, a common sequence being tonsillitis, tonsillar or peritonsillar abscess, cervical lymphadenitis, cervical abscess and, finally, thrombophlebitis in the internal jugular vein. Frankel (1925) noted that this series was a frequent precursor of septicaemia, and for a time ligation of the internal jugular vein was recommended. Kissling, in 1929, attempted this but 10 of his 12 cases died.

Alimentary Tract. In 26 of the recorded cases septicaemia followed lesions of the alimentary tract. Appendicitis, pyelophlebitis and liver abscess frequently preceded septicaemia. Such a sequence was not uncommon before antibiotics. Although the organisms could not always be isolated it is possible that bacteroides were, in fact, the offending organisms because the clinical picture resembles so closely that of proven bacteroides septicaemia.

Complications of Bacteroides Infection. The complications of bacteroides infection are detailed in Table 1. The frequency of abscess formation in the serous cavities, liver and lung is most striking although the formidable list of complications is probably incomplete as some of the recorded cases lacked detail.

TABLE 1

COMPLICATIONS OF BACTEROIDES INFECTIONS

Septicaemia	173
Anaemia	45
Jaundice	61
Thrombophlebitis	26
Abscess in subcutaneous tissues	50
Peritonitis and intra-abdominal abscess	23
Liver abscess	53
Pulmonary abscess and pneumonia	70
Pleural effusion and empyema	36
Pericardial effusion	9
Endocarditis	5
Meningitis	9
Intracranial abscess	5
Arthritis	22
Osteomyelitis	8
Renal abscess	1
Prostatic abscess	1

CLINICAL FEATURES. The clinical features conform to a regular pattern. (1) Symptoms and signs of the primary lesion; (2) a period of apparent recovery; (3) symptoms and signs of a spreading infection at the site of the original lesion; (4) abrupt onset of septicaemia with rigor, profuse sweating, anaemia and jaundice; (5) symptoms and signs of metastatic infective lesions.

The dramatic picture presented by the first patient and the clarification of the features of the infection from cases recorded in the literature suggested that bacteroides infection was not uncommon and that its occurrence was frequently not recognized. Suspicion of this complication from the clinical features and the routine setting up of anaerobic cultures when suspicion arose has led to the recognition of six further cases (four in children) within a period of 18 months. The case records follow:

Case 2 (Fig. 4). A girl aged 11, with a history of recurrent abdominal pain suggestive of mesenteric adenitis, was admitted in an acute attack. As appendicitis could not be excluded, laparotomy was carried out and the diagnosis of mesenteric adenitis was confirmed. A normal appendix was removed.

A minor post-operative chest infection responded quickly to penicillin and physiotherapy. For two weeks following operation the only complaint was occasional vague abdominal pain for which no cause could be found.

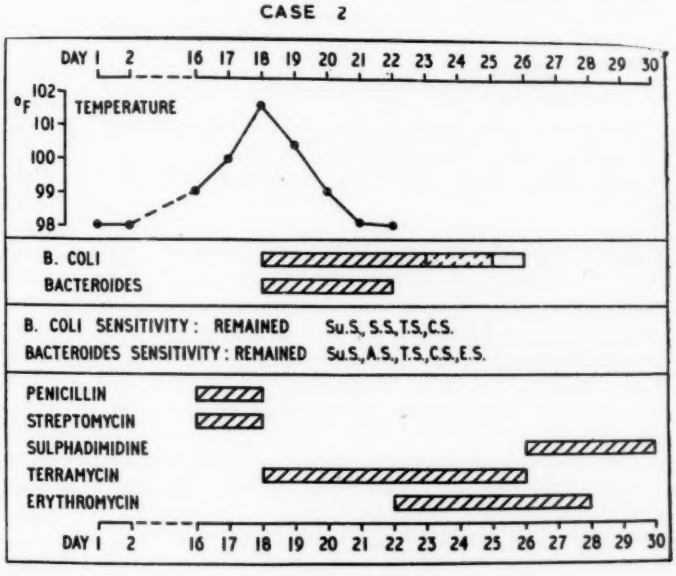
CASE 2
DAY 1 2 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
°F 102 101 100 99 98
TEMPERATURE
B. COLI
BACTEROIDES
B. COLI SENSITIVITY: REMAINED Su.S, S.S, T.S, C.S.
BACTEROIDES SENSITIVITY: REMAINED Su.S, A.S, T.S, C.S, E.S.
PENICILLIN
STREPTOMYCIN
SULPHADIMIDINE
TERRAMYCIN
ERYTHROMYCIN
DAY 1 2 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

FIG. 4.—Case 2, girl aged 11 years.

On the fifteenth post-operative day pain became localized to the gridiron incision, where some bruising was apparent. The temperature was 99° F. but the patient did not appear ill. Penicillin and streptomycin were administered but over the next 48 hours the temperature began to swing and there was profuse sweating. The child became pale and slightly icteric, the abdominal bruising increased and a mass formed in the pelvis and the right iliac fossa.

The possibility of a bacteroides infection was appreciated and terramycin therapy was begun. The gridiron incision was reopened and the muscles of the anterior abdominal wall found to be black and necrotic with collections of evil-smelling pus. As the exposure was not entirely satisfactory a paramedian incision was made and the right rectus muscle was also found to be black and oedematous, even above the level of the umbilicus.

A large, foul-smelling abscess in the pelvis and the right iliac fossa was emptied and drainage established through a suprapubic stab incision. Leakage from the appendix stump could not be demonstrated. The gridiron incision was left open with a hydrogen peroxide pack and the paramedian closed with a few interrupted sutures.

Bacteriological examination confirmed the presence of a bacteroides infection and septicaemia after four days' incubation. Subsequently repeated examinations of the purulent discharge showed no change in the sensitivity to antibiotics.

Terramycin was continued for eight days, and, for the latter half of this course, erythromycin was also given initially to prevent staphylococcal enteritis and later because the organisms were shown to be highly sensitive to it. Therapy was tailed off with sulphadimidine for two weeks.

The temperature fell rapidly but despite transfusion the subsequent progress was slow. On discharge six weeks after admission the wounds had healed but there was still considerable induration in the anterior abdominal wall.

A normal appendix was removed. The case illustrates two important points: (1) the delay in the development of the complication and (2) the administration of an antibiotic before its development.

Case 3 (Fig. 5). A girl aged 11 was admitted with a 12-hour history of colicky abdominal pain, later becoming constant. There was associated nausea and vomiting. She had had two previous attacks of pain.

On examination, there was tenderness in both iliac fossae, maximal on the right side. There was no rebound tenderness but she was very tender on rectal examination.

A diagnosis of appendicitis was made and at operation an acutely inflamed appendix was removed and the wound closed without drainage.

Two days later the temperature began to swing and was considered to be due to wound infection. Penicillin and streptomycin were administered.

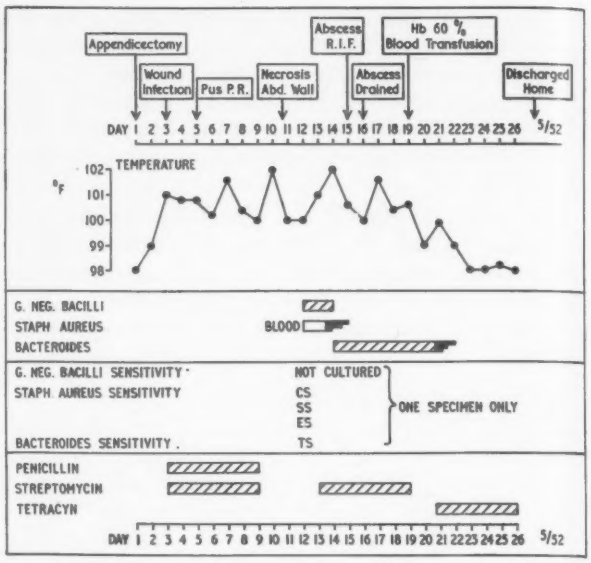

FIG. 5.—Case 3, girl aged 11 years.

Five days post-operatively the patient developed diarrhoea and was found to be very tender in the pouch of Douglas. Twelve days post-operatively bruising became apparent around the wound and probing liberated about 60 ml. of dark blood which, on culture, proved to contain bacteroides. Fourteen days post-operatively it was decided to drain the abscess which was found to extend into the pelvis. Six hundred millilitres of pus were liberated. A drain was left down into the pelvis. In addition, tetracycline was given.

The subsequent progress was steady and the girl was discharged five weeks after admission.

This was a case of acute appendicitis, presenting again (1) the delay in the full development, (2) the good response to adequate drainage, (3) the failure to respond to penicillin and streptomycin but a response to tetracycline.

Case 4 (Fig. 6). A man aged 30 was admitted with a 12-hour history of pain moving from the right hypochondrium to the right iliac fossa with nausea and vomiting. There was one previous attack.

Examination revealed tenderness and rigidity in the right iliac fossa. A diagnosis was made of acute appendicitis and at operation a pelvic, gangrenous appendix was removed and the wound closed with drainage of the peritoneal cavity. Penicillin was administered.

Post-operatively the drain discharged evil-smelling grey pus and bacteriological examination revealed a mixed growth of β haemolytic streptococci and bacteroides. The latter was insensitive to penicillin.

The temperature began to swing despite apparent adequate drainage and a pelvic abscess was found. Terramycin was given and the patient recovered without surgical or spontaneous drainage of the abscess.

This was a case of gangrenous appendicitis presenting (1) abscess collections despite drainage; (2) once again penicillin therapy, probably administered incorrectly for an alimentary infection; (3) the delay in appearance of collections.

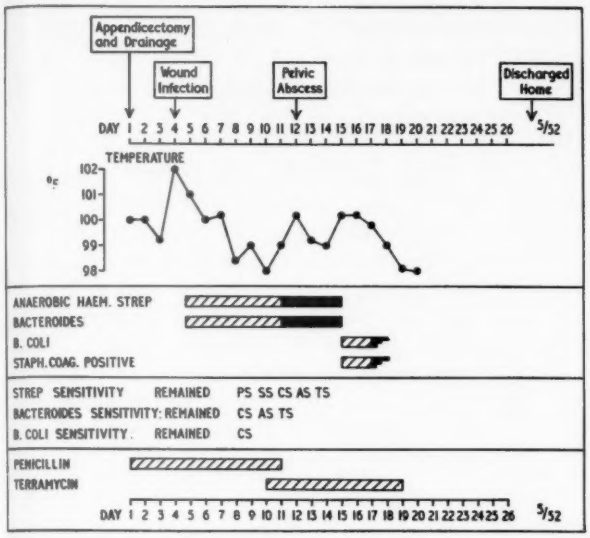
Appendicectomy and Drainage
Wound Infection
Pelvic Abscess
Discharged Home
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
5/52
TEMPERATURE
°F
102
101
100
99
98
ANAEROBIC HAEM. STREP
BACTEROIDES
B. COLI
STAPH. COAG. POSITIVE
STREP SENSITIVITY REMAINED PS SS CS AS TS
BACTEROIDES SENSITIVITY: REMAINED CS AS TS
B. COLI SENSITIVITY. REMAINED CS
PENICILLIN
TERRAMYCIN
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
5/52

FIG. 6.—Case 4, man aged 30 years.

Case 5 (Fig. 7). A boy aged 3 was admitted with a history of a cold and cough for one week and pain in the right iliac fossa for 24 hours. In addition he had nausea and vomited.

On examination there was tenderness in the right iliac fossa with guarding over the whole lower abdomen.

A diagnosis of acute appendicitis was made and at operation a perforated appendix was removed from a retrocaecal extraperitoneal position. The wound was not drained.

Three days later he began to vomit and the temperature began to swing. The wound showed bruising. He looked toxic, the possibility of a bacteroides infection was considered, and drip and suction and terramycin therapy were instituted.

Eight days after operation he developed a superficial and deep venous thrombosis in the right leg. Heparin was administered for five days.

On the eleventh day erythromycin was given instead of terramycin because of the appearance of an abscess of the anterior abdominal wall.

On the 15th day the abdominal abscess discharged spontaneously with a copious flow of brownish, foul-smelling pus. Four weeks after operation the wound had almost healed and the oedema of the right leg had subsided. Eight weeks after appendicectomy he was discharged home.

This case of perforated appendicitis illustrated two factors: (1) local spreading infections after a delay of some two weeks, (2) evidence of thrombophlebitis.

Case 6 (Fig. 8). A man aged 32 was admitted with two weeks' history of suprapubic pain spreading to the right iliac fossa. He had felt sick but had not vomited. Two days before admission the pain became more severe and was located just to the right of the umbilicus.

On examination his temperature was 101° F. and a tender swelling was palpated in the right iliac fossa with overlying guarding. A diagnosis of appendicitis with abscess formation was made and laparotomy was carried out. The mass was found to be a large abscess within the mesentery of the mid-ileum surrounded by coils of small bowel. The adjacent ileum was thickened and rigid. A biopsy of the abscess cavity wall was taken. The bacteriological report showed bacteroides.

His immediate post-operative progress was very stormy with a peritonitis which was treated by drip and suction and penicillin and streptomycin.

On the fifth post-operative day terramycin was substituted because of the patient's failure to respond.

On the seventh post-operative day the patient became severely shocked very suddenly. This was countered with a massive intravenous transfusion of seven parts plasma, and one of blood. In the same evening the patient developed profuse diarrhoea. Later bacterio-

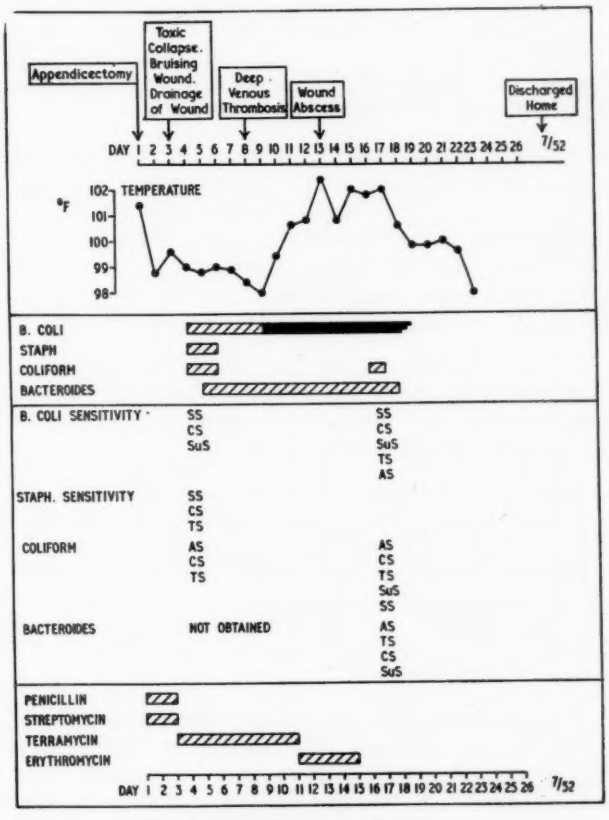
Appendicectomy
Toxic Collapse. Bruising Wound. Drainage of Wound
Deep Venous Thrombosis
Wound Abscess
Discharged Home
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
7/52
TEMPERATURE
°F
102
101
100
99
98
B. COLI
STAPH
COLIFORM
BACTEROIDES
B. COLI SENSITIVITY · SS CS SuS / SS CS SuS TS AS
STAPH. SENSITIVITY SS CS TS
COLIFORM AS CS TS / AS CS TS SuS SS
BACTEROIDES NOT OBTAINED / AS TS CS SuS
PENICILLIN
STREPTOMYCIN
TERRAMYCIN
ERYTHROMYCIN
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
7/52

FIG. 7.—Case 5, boy aged 3 years.

logical reports showed this to be a staphylococcal enteritis; the staphylococci were erythromycin-resistant.

On the eighteenth post-operative day, when the patient had begun to improve, he started complaining of abdominal pain and the temperature began to swing. A wound abscess was obviously gathering and required operative drainage on the twentieth day. The wound was left open and was healed one month later.

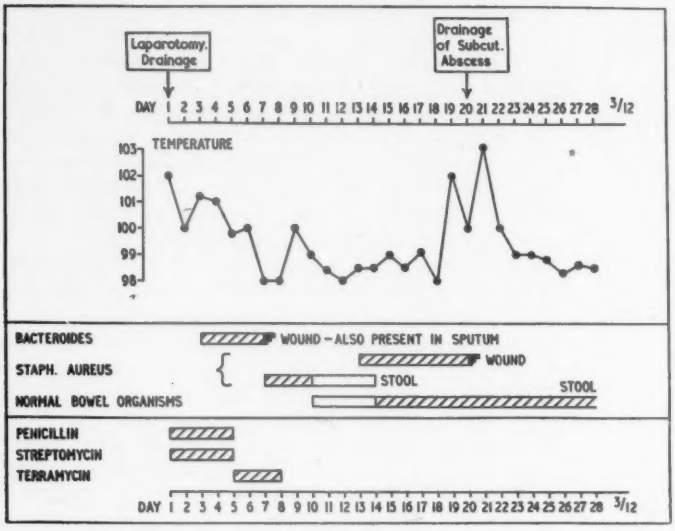
Laparotomy. Drainage
Drainage of Subcut. Abscess
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 3/12
TEMPERATURE
103
102
101
100
99
98
BACTEROIDES
WOUND – ALSO PRESENT IN SPUTUM
STAPH. AUREUS
WOUND
STOOL
NORMAL BOWEL ORGANISMS
STOOL
PENICILLIN
STREPTOMYCIN
TERRAMYCIN
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 3/12

FIG. 8.—Case 6, man aged 32 years.

This case, previously reported by Dudley and MacLaren (1956), is interesting from many points of view. The points requiring emphasis are: (1) A bacteroides bowel infection present from the onset; (2) later development of staphylococcal enteritis; (3) final development of a wound infection on the 18th day which responded well to open drainage.

Case 7 (Fig. 9). A boy aged 4 was admitted with a two weeks' history of tonsillitis for which he had received penicillin from his own doctor. Despite this a mass had developed in the right side of the neck.

On examination the temperature was 98·8° F., the fauces were inflamed. On palpation a large fluctuant swelling was found in the right posterior triangle, 12·5 cm. × 7 cm. The swelling extended from the post-auricular region, anteriorly, to the angle of the mandible and, posteriorly, to the occiput.

After adequate drainage of the abscess his condition gradually improved until he was discharged on his sixth week in hospital.

The sequence was tonsillitis followed by lymphadenitis and abscess. This case is of interest for three reasons: (1) It is the type of case most commonly reported; (2) failure to respond to penicillin; (3) anaemia, haemoglobin falling to 70%.

Conclusion

Diagnosis. The diagnosis of bacteroides infection and septicaemia is not difficult if its possible occurrence is kept in mind. Confirmation is obtained by careful bacteriological studies. The initial film and prolonged anaerobic culture will reveal the organisms.

Treatment. The principles of treatment can be summarized briefly as follows: (1) Open treatment of infected wounds; (2) prompt surgical drainage of any purulent collection; (3) the exhibition of a broad-spectrum antibiotic, usually more effective than penicillin or streptomycin; (4) continuous bacteriological control, since sensitivity to antibiotics may change with great rapidity; (5) maintenance of haemoglobin and of general nutrition.

Prognosis

Bacteroides infection has been attended hitherto by a high mortality and serious morbidity. This is well-illustrated by the cases presented, five of the seven being under the age of 12 years.

The mortality and morbidity can be reduced only when the diagnosis is made quickly and appropriate treatment is started in good time. Bacteriological confirmation may take as long as four days, and, if the infection is suspected on clinical grounds, treatment should be begun immediately without awaiting the bacteriological report.

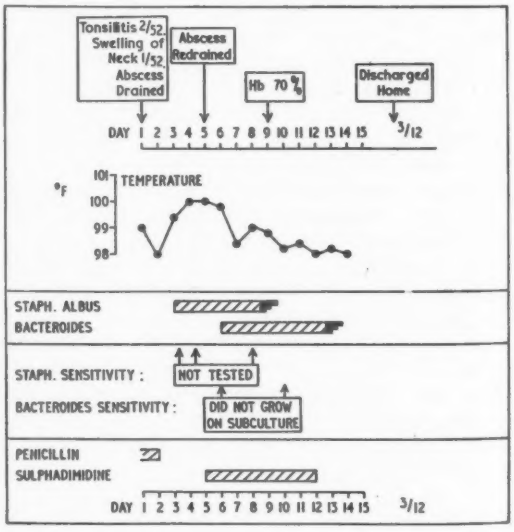

FIG. 9.—Case 7, boy aged 4 years.

From the recorded cases and the experience gained from the treatment of the seven patients whose histories are described it seems justifiable to conclude that surgeons and bacteriologists are insufficiently aware of the occurrence of anaerobic infection by this group of organisms and the late development of septicaemia. Since so much can be gained from early treatment it is imperative that anaerobic cultures are not discarded after 48 hours' incubation when the disease is suspected on clinical grounds.

I am grateful to Mr. J. J. Mason Brown, Mr. F. H. Robarts, Mr. I. S. Kirkland, Mr. H. A. F. Dudley and Mr. Ian Campbell for asking me to see and treat patients under their charge.

References

Alston, J. M. (1955). *Brit. med. J.*, **2**, 1524.
Dudley, H. A. F. and MacLaren, I. F. (1956). *Lancet*, **2**, 1182.
Frankel, E. (1925). Cited by Kissling, K. (1929). *Münch. med. Wschr.*, **76**, 1163.
Gunn, A. A. (1956). *J. roy. Coll. Surg. Edinb.* **2**, 41.
King, A. B., Conklin, S. D. and Collette, T. S. (1952). *Ann. intern. Med.*, **37**, 761.
Kissling, K. (1929). *Münch. med. Wschr.*, **76**, 1163.

BOOK REVIEWS

The Metabolic Response to Neonatal Surgery. By PETER PAUL RICKHAM. (Pp. ix+93; illustrated. 40s.) Harvard University Press; London: Oxford University Press. 1957.

This monograph, sponsored by the Commonwealth Fund and published by the Harvard University Press, puts into print work which the author has been carrying out for some years.

Mr. Rickham courageously set out, by using the technique of a careful metabolic balance, to study the response of the neonate to surgery. Anyone who has attempted to carry out experiments of this character will know the enormous amount of work that goes into such a task and he and his helpers are to be congratulated on having made so complete a study of so many infants as they have.

After two brief introductory chapters devoted to an historical survey and to technical methods, he describes in adequate detail eight infants who have had various operations, upon whom complete data are available from the pre-operative phase to either convalescence or death. In each case the clinical story and the results of the balance studies are given and then follows a brief analysis of the findings. Various types of cases have been chosen, from the premature to the relatively mature 3-week-old child, with ranges of operation from the mildly traumatic one to a severe operation entailing a second a few days later. He then gives a general discussion which is commendably lucid and by no means lengthy, in which the factors involved in the response to trauma are discussed and compared with the type of response in the adult.

It is abundantly clear that the neonate responds very differently from the adult to surgical trauma. As a result of this difference, the neonate appears to be able to withstand surgical insult very much better than would have been expected. As an example, whereas the adult loses considerable quantities of potassium, the amount of potassium lost by the neonate is relatively small and appears to be no more than the potassium lost in the catabolism of the tissues during starvation.

The final chapter is on practical applications and in this the author leaves behind the various speculations as to possible reasons for the changes that have been found and crystallizes his experiences in the handling of the metabolic problems of neonatal surgery in an extremely valuable chapter. Whatever one may consider to be the explanations of the metabolic puzzles which he has been describing, there can be no doubt whatsoever that the instructions that he gives for handling these problems are the best available at our present state of knowledge.

Some of his more important points can be summarized: loss of body weight up to 5 or 10% is normal for the neonate, and loss up to 20% can be tolerated without harm. The majority of this loss of weight is water and metabolite fat. Similarly, calories are not so vitally important to the neonate as to the older infant. In dealing with the fluid requirements, while it is important to correct dehydration pre-operatively it must be recognized that the amount of fluid required subsequently is not great and there is more danger of drowning a child by overhydration than of damaging it by dehydration. Equally as important is the necessity of restricting the amount of sodium and chloride given and he recommends that normally no stronger solution than N/5 saline should be given, except when marked salt loss has occurred, when small quantities of N/2 saline may be given. Potassium only needs to be given when there is delay in feeding or large quantities of fluid have been removed by gastric suction, and even then only small amounts of potassium supplement are recommended. However, the author stresses the impossibility of adequate control of the post-operative phase by rule of thumb methods and he states categorically that unless facilities for a rapid service from the laboratory for the necessary blood analyses by micro methods is available neonatal surgery should not be attempted.

For those who are interested in the technicalities of intracellular and extracellular water and electrolyte behaviour, a study of his eight cases is highly rewarding, and, though certain problems receive an answer, an even greater number of problems as to how various changes have occurred are presented, and these make one entirely agree with the author's statement in his summing up that 'We know as yet very little about the many physiological and pathological changes which we initiate when operating on newborn infants'.

Les Malformations Congénitales du Poumon. By ANDRÉ BRETON and OLIVIER DUBOIS. (Pp. 140; 18 figures plus 18 plates. Frs. 2,200.) Paris: G. Doin. 1957.

Until recently, congenital malformations of the respiratory tract have mainly interested anatomists and embryologists; in consequence, there is little mention of them in most standard clinical textbooks. However, with more frequent and improved radiological investigation and the development of thoracic surgery, such malformations have acquired increased importance. This monograph brings together a useful collection and classification of information from widely dispersed sources. After a good account of the development of the respiratory tract, both *in utero* and post-natally, there are sections on pulmonary agenesis and hypoplasia, accessory and sequestrated lobes, bronchogenic and air-containing cysts and anomalies of the pleural fissures and bronchi. The illustrations are adequate and the bibliography is very comprehensive.

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EDITORS
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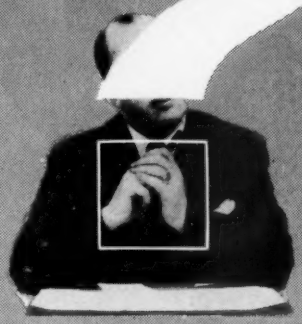

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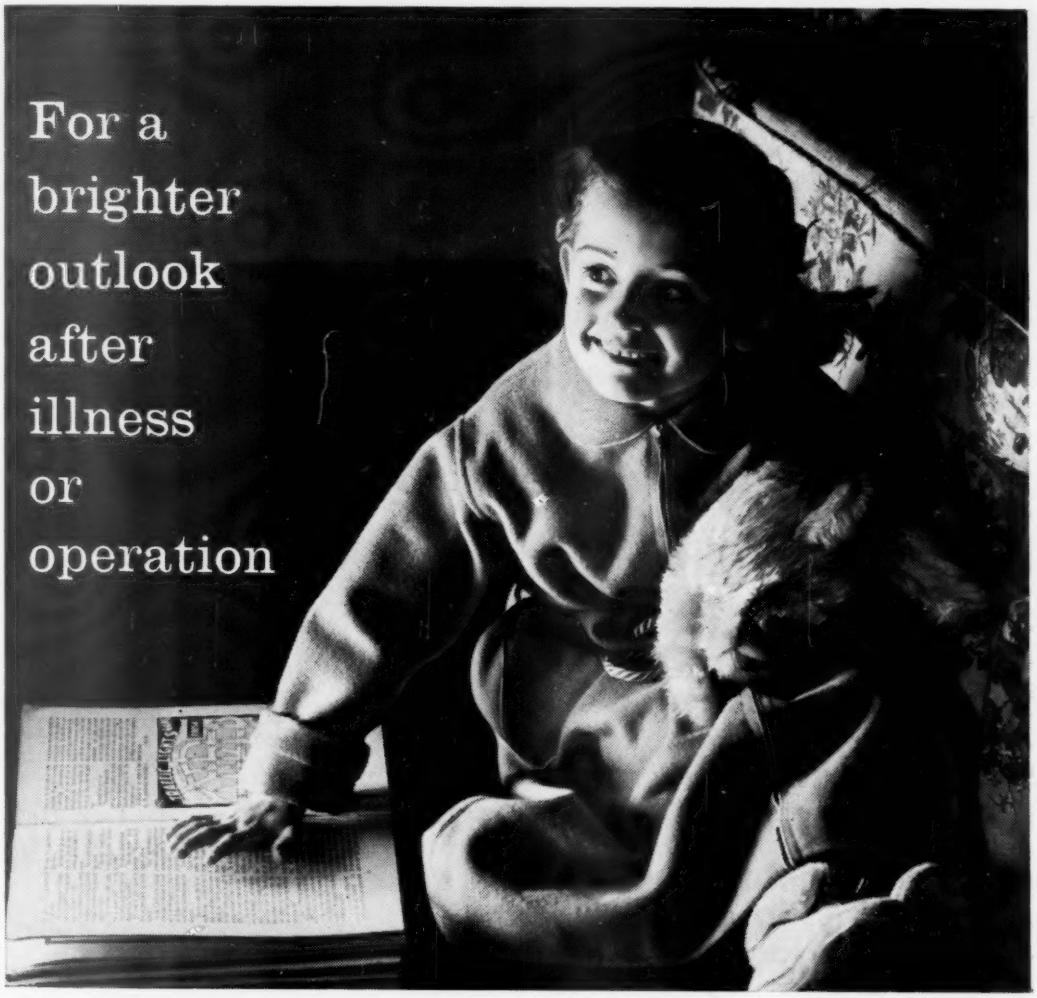

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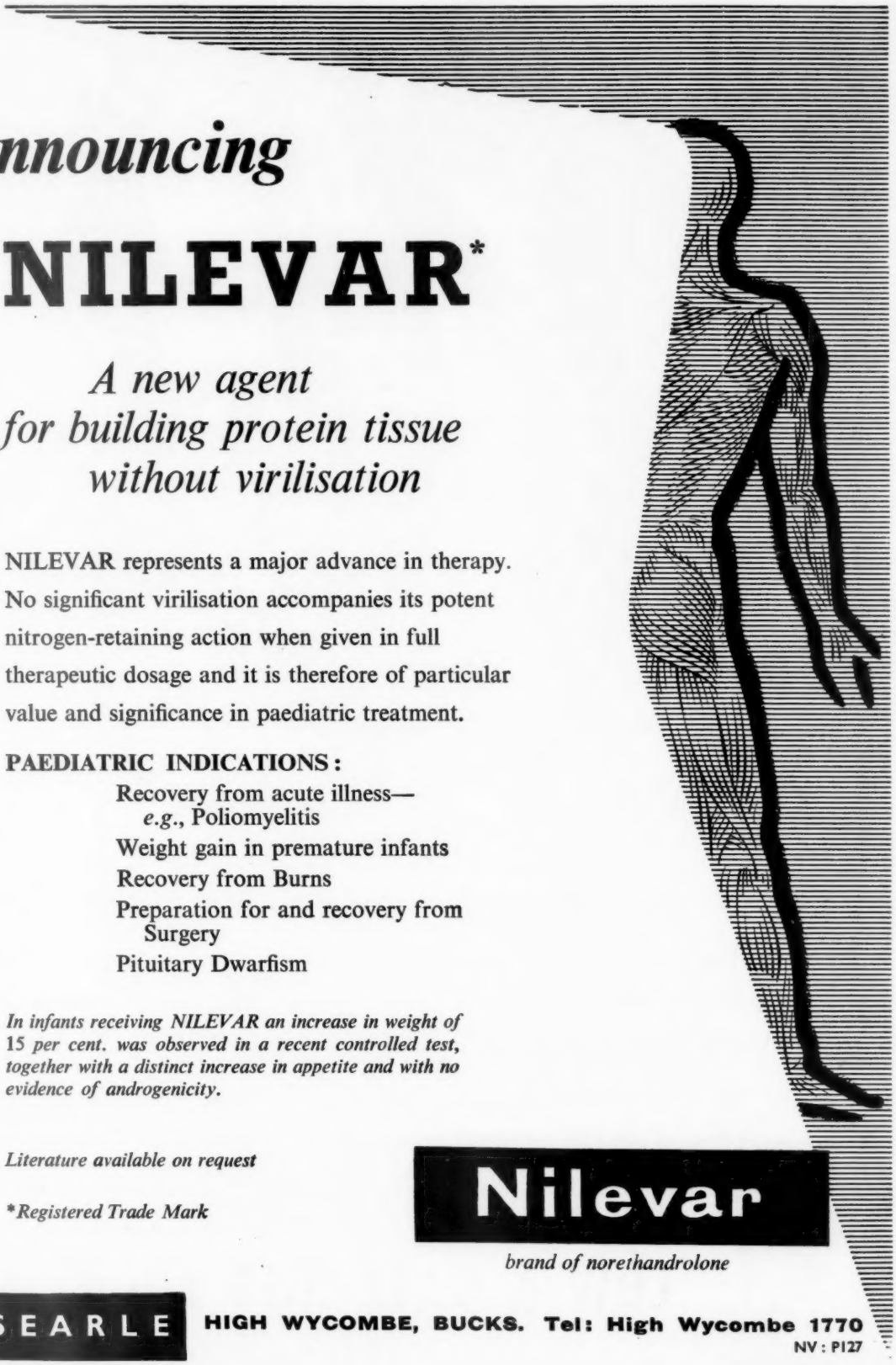

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NUFFIELD INSTITUTE FOR MEDICAL RESEARCH

Research Fellowships

The Nuffield Foundation, as an experiment, is prepared to offer one research fellowship annually in each of the three years 1958, 1959 and 1960, tenable at the Nuffield Institute for Medical Research at Oxford, to enable a suitably qualified person who intends to follow an academic career in obstetrics or paediatrics in the United Kingdom to concentrate for a year on animal experiments directly related to basic physiology or pharmacology in the foetus or the new-born.

Each fellowship will be tenable for one year and is limited to graduate of medicine of a University within the British Commonwealth. Normally a candidate should have completed an appointment as Registrar (or its equivalent) in an approved department of obstetrics or paediatrics, and also have obtained the higher qualification appropriate to his chosen speciality. The stipend will be within the approved range of salaries for Senior Registrars under the National Health Service. Applications for the award beginning in 1958 must be received before 15th February, 1958 by the Director, The Nuffield Foundation, Nuffield Lodge, Regent's Park, N.W.1, from whom full particulars and application forms can be obtained.

L. FARRER-BROWN
Director of the Nuffield Foundation

pleasant-tasting

Paladac

liquid

vitamin

supplement

Children take Paladac without fuss or bother because it "tastes good".

Mothers like to give it because Paladac is readily accepted, flows freely, needs no refrigeration, and may be added to milk, fruit juice and other foods, or taken direct from a teaspoon.

Doctors can prescribe Paladac with confidence since it provides a reliable daily source of vitamins—one 4 c.c. teaspoonful supplies 7 vitamins in amounts exceeding minimum daily vitamin requirements.

Primarily intended for the 3-10 age-group, Paladac is equally suitable for adolescents and adults where liquid medication may be preferred.

Paladac is supplied in bottles of 4 and 16 fl. oz.

Each teaspoonful (4 c.c.) contains:—Vitamin A 5,000 units, Vitamin D 1,000 units, Vitamin B_1 (Aneurine Hydrochloride) 3 mg., Vitamin B_2 (Riboflavin) 3 mg., Vitamin B_6 (Pyridoxine Hydrochloride) 1 mg., Nicotinamide 20 mg., Vitamin C (Ascorbic Acid) 50 mg.

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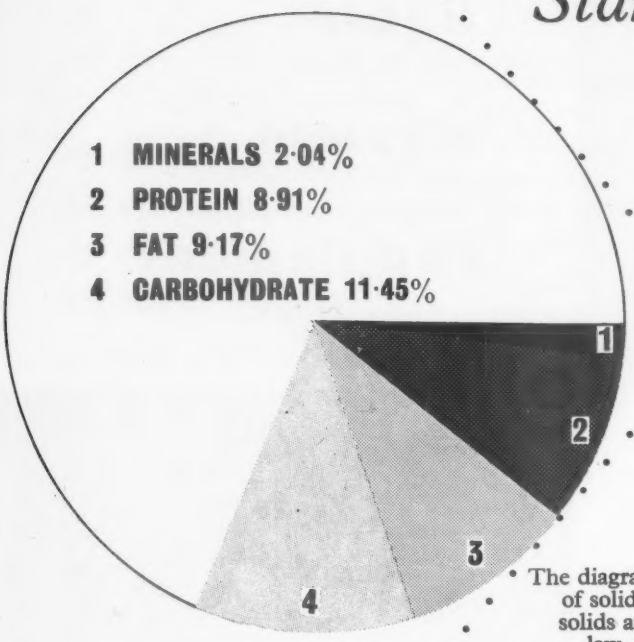
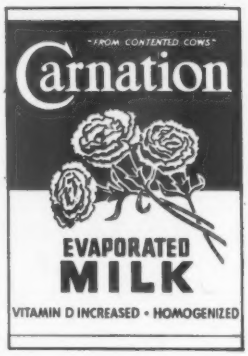
70

Carnation Milk *for infant feeding*

The advantages of *Standardisation*

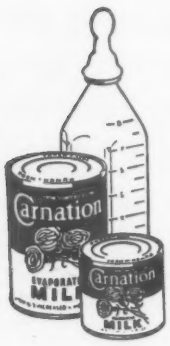




The diagram above shows the percentage of solids in Carnation Milk. The total solids are standardised, as required by law, to a minimum of 31%. Of this figure 9% must be butterfat. Previous Carnation advertisements have demonstrated that, chemically and physically, ordinary milks cannot compete with the range of tolerance and digestibility of the proteins and butterfat in Carnation Milk. These superiorities in an infant food are enhanced by the uniformity obtained by standardisation.

Uniformity in practice means :—

1. Constant calorie value. 2. Accuracy and ease of measurement. 3. Control of intake where necessary. 4. Precision in dilution. 5. A milk of known value at all times — and available everywhere.

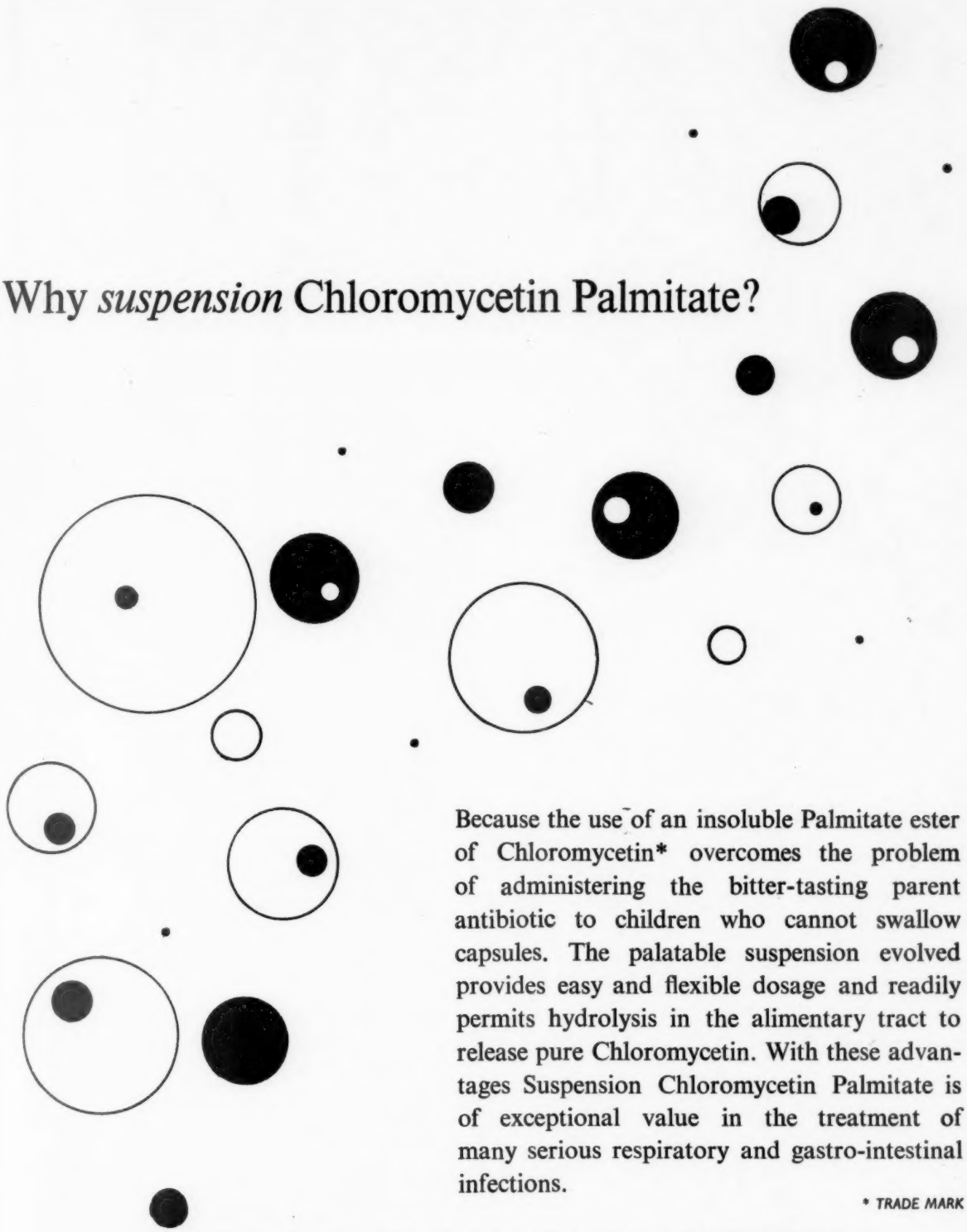


Other attributes of Carnation Milk are:
— Safety, because of sterilisation *after* the Carnation cans are sealed — Hypo-allergenic properties — Homogenisation — Prophylactic D3.

"The Feeding of Infants" — a book specially prepared for doctors together with reprints of clinical investigations and Carnation feeding charts are available from: Medical Dept., General Milk Products Ltd., Bush House, Aldwych, London, W.C.2.

CARNATION MILK *"from Contented Cows"*

Why *suspension* Chloromycetin Palmitate?



Because the use of an insoluble Palmitate ester of Chloromycetin* overcomes the problem of administering the bitter-tasting parent antibiotic to children who cannot swallow capsules. The palatable suspension evolved provides easy and flexible dosage and readily permits hydrolysis in the alimentary tract to release pure Chloromycetin. With these advantages Suspension Chloromycetin Palmitate is of exceptional value in the treatment of many serious respiratory and gastro-intestinal infections.

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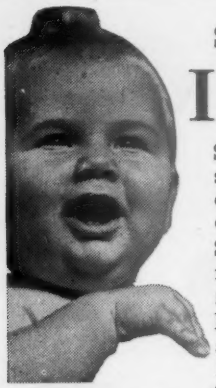

Safety, simplicity and digestibility in

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Easily Digested—Digestibility depends upon low curd tension and small curd particle size. The sterilization by heat of Libby's Milk is far more effective than is boiling in lowering curd tension.

BUT curd particle size is an even more important index of digestibility than is curd tension, as shown by Doan and co-workers in the United States. Libby's Evaporated Milk, reconstituted with water and curdled with rennin, which approximates conditions occurring in the infant's stomach, remains liquid with suspension of extremely fine curds, similar to human milk, and much finer than curd from boiled or any other kind of cow's-milk.

* Please send for the booklet entitled 'Infant Feeding with Evaporated Milk'.

A
B
C

Photomicrographs showing comparison of curds from:
A Human Milk
B Libby's Evaporated Milk mixed with 1½ times its volume of water
C Pasteurized Milk
Each specimen was curdled by the addition of rennin. During the precipitation the milks were stirred constantly to simulate conditions in a baby's stomach.

Libby's

Full Cream Evaporated **MILK**

Libby's Infant Feeding Department welcomes enquiries

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MARMITE yeast extract

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MODERN PROBLEMS IN PEDIATRICS-Vol. II

Symposium on Physiology and Pathology of Digestion in Infancy

Edited by

A. HOTTINGER and F. HAUSER, Basel

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Titles of some of the articles: Development of Intestinal Flora in the Breast-Fed Infant. Observations on Fat Absorption in Infants. Metabolic Disturbances in Infantile Malnutrition. Proteins in Malnutrition. The Effect of Food and Growth on the Stability of the Intestinal Environment.

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